Int. J. Pharm. Investigation, 2026; 16(1):1-11.
https://www.jpionline.org

Review Article

Anti-Parkinson Drug Levodopa: It's Novel Delivery Systems, Preclinical and Clinical Studies: A Review

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ABSTRACT

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons and the presence of Lewy body pathology. Its prevalence increases with age, affecting approximately 1-2% of individuals over 60 years old. While PD is primarily idiopathic, genetic predisposition and environmental factors such as smoking, caffeine intake, pesticide exposure, and heavy metal accumulation contribute to its etiology. The disease manifests through motor symptoms like tremors, bradykinesia, and postural instability, alongside non-motor symptoms such as cognitive decline and sleep disturbances. Levodopa (LD) remains the gold standard treatment for PD, as it effectively restores dopamine levels in the brain. However, long-term administration results in complications such as motor fluctuations and dyskinesia. Advances in levodopa therapy have led to the development of novel drug delivery systems, including nanoparticles, liposomes, and microemulsions, which aim to improve its bioavailability and reduce adverse effects. Combination therapies with COMT and MAO-B inhibitors have also been introduced to enhance levodopa's efficacy and prolong its therapeutic effects. Gene-editing technologies like CRISPR-Cas9 and stem cell therapies are being explored as potential avenues for modifying PD progression and optimizing levodopa utilization. *Ex vivo* and *in vivo* studies have provided insights into levodopa's pharmacokinetics and efficacy. Studies using animal models have demonstrated improved levodopa delivery through alternative routes, such as intranasal administration, which showed significantly higher brain uptake compared to oral administration. Investigations on gut microbiome interactions have also suggested their role in influencing levodopa absorption and metabolism. Emerging therapeutic approaches, including Deep Brain Stimulation (DBS), immunotherapy, and virtual reality-based rehabilitation, are being explored in combination with levodopa to enhance its benefits. Functional imaging techniques like fMRI and PET scans have provided valuable insights into levodopa's effects on brain activity, paving the way for more individualized treatment strategies. Furthermore, novel formulations such as transdermal patches, buccal tablets, and duodenal infusions are being developed to ensure sustained levodopa release and minimize fluctuations. This review article provides an overview of Parkinson's disease, its clinical features, etiology, and advancements in levodopa therapy. By examining innovative drug delivery strategies, combination treatments, and emerging research trends, we highlight potential avenues for improving patient outcomes and addressing the limitations of current PD management strategies.

Keywords: Gene-Editing, Gut Microbiome, Immunotherapy, Intranasal Delivery, Nanocarriers, Sustained Release Formulations.

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Received: 14-05-2025;
Revised: 24-07-2025;
Accepted: 05-09-2025.

INTRODUCTION

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons and the presence of Lewy body pathology. The classic motor symptoms include resting tremors, low amplitude movement (hypokinesia) or no movement (akinesia), inflexibility, and postural instability (Fahn, 2008). Over time, reduced neurotransmitter levels, oxidative stress, mitochondrial dysfunction, and disrupted protein homeostasis contributes to worsening of the disease symptoms in older individuals (John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK *et al.*, 2018).

Levodopa (LD) is the direct precursor to dopamine and serves as an effective prodrug, enabling Central Nervous System (CNS) penetration and delivering dopamine. It has long been, and

DOI: 10.5530/ijpi.20260415

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

continues to be, the gold standard treatment for PD, particularly in its early stages (Blandini, F. and Greenamyre, J.T., 1999). Nevertheless, chronic long-term treatment with LD causes motor complications (on-off phenomenon) in most patients. In addition, dyskinesia may occur due to excess dopaminergic tone (Ahlskog and Muenter, 2001).

LD is a very effective treatment in the early stages of PD ('Levodopa and the Progression of Parkinson's Disease', 2004). When used in combination with carbidopa, a decarboxylase inhibitor, its efficacy doubles. Carbidopa acts on peripheral decarboxylase and cannot cross blood-brain barrier. Carbidopa's primary function is to reduce the peripheral breakdown of Levodopa (LD), thereby minimizing the drug's systemic side effects (Hagan *et al*., 1997). This review discusses epidemiology, etiology, clinical features, various approaches in treatment of PD, several novel drug delivery systems with anti-Parkinson drugs, preclinical and clinical studies investigations.

Epidemiology

PD affects 1-2 individuals per 1,000 people at any given time. Its prevalence increases with age, impacting approximately 1-2% of those over 60. Around 5-10% of patients have a genetic predisposition to the condition (Shastry, 2001). The occurrence of PD has increased twofold in the last 25 years. This disease is a common condition which has affected roughly 6·1 million people worldwide in 2016 (Bloem *et al*., 2021). Global projections from 2019 indicated that more than 8.5 million individuals are living with PD. In 2019, PD accounted for 5.8 million disability-adjusted life years, representing an 81% rise since 2000, and resulted in 3,29,000 fatalities, more than doubling since 2000. The condition is more prevalent in men than in women (Tysnes and Storstein, 2017). Table 1 shows the epidemiology of PD.

CLINICAL FEATURES OF PD

PD is recognized for its movement-related symptoms-shaking, stiffness, and slowness of movement-frequently followed by balance issues as the condition advances. However, non-motor signs such as reduced sense of smell, constipation, and sleep disturbances may emerge years before the motor symptoms. The subsyndromal stage may commence 12-14 years prior to diagnosis, with timely signs such as tremor, balance issues, and fatigue indicating higher risk. Early intervention during this phase could be crucial for treatment, as significant dopaminergic neuron loss occurs even early in the disease (Colcher and Simuni, 1999).

Diagnosis is determined by slowness of movement and either shaking or stiffness, with uneven symptoms and a positive reaction to levodopa reinforcing the diagnosis. PD is highly variable, with two subtypes: tremor-dominant and non-tremor-dominant, which differ in symptoms, response to treatment, and prognosis (Colcher and Simuni, 1999).

As PD progresses, both motor and non-motor symptoms worsen, along with aggravations like abnormal movement (dyskinesia), psychosis, and derangement, which can make management difficult. Non-motor symptoms, which is inclusive of nonpartisan dysfunction and cognitive issues, significantly affect quality of life and foresee nursing home admission (Colcher and Simuni, 1999).

Etiology

PD is a disorder shaped by both congenital and ecological factors. Life span is one of the leading significant determinant for PD. Symptoms typically manifest around 60 years old (Lees *et al*., 2009). The occurrence increases with age, reaching 93.1 cases per 100,000 person-years in individuals aged 70 to 79 years (De Rijk *et al*., 1995).

Smoking

Cigarette use has been linked to a decreased risk of developing PD a connection supported by numerous investigations. A large meta-analysis involving 44 case-control and eight prospective studies found an inverse relationship between puffing and PD, with current smokers showing a significantly depleted risk. Diverse research has yielded similar findings, implying long-term or heavy smokers are more likely to develop PD (Grandinetti *et al*., 1994). Although the exact cause of this protective effect remains uncertain, one possibility is that nicotine activation of nicotinic receptors in dopaminergic neurons may offer neuroprotection. However, it is also suggested that people with PD may be less inclined to smoke due to lower dopamine levels, which could make them less susceptible to addiction (Breckenridge *et al*., 2016).

Caffeine

Multiple studies suggest that caffeine, especially from coffee, may lower the risk of developing Parkinson's Disease (PD). Caffeine functions as an adenosine A2A receptor antagonist (Ross, 2000), which has demonstrated neuroprotective outturn in PD models (J.-F. Chen *et al*., 2001). Coffee drinkers have been found to possess a 25% reduced risk of PD, with studies reporting a relative risk ranging from 0.45 to 0.80 compared to non-coffee drinkers (Ascherio *et al*., 2001). Tea drinkers also show a reduced risk. However, the precise role of caffeine in intercepting PD remains unclear, with some studies indicating that the effect may be more pronounced in men than women. In post-menopausal women, caffeine's influence might depend on hormone substitution therapy, as estrogen can slow caffeine metabolism, affecting its potential impact on PD risk (Hernán *et al*., 2002).

Pesticides, Herbicides and Heavy metals

In 1983, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was considered to be associated with PD after individuals developed PD manifestation from injecting a drug contaminated with it (Xu *et al*., 2006). MPTP is metabolized into MPP+

(1-methyl-4-phenylpyridinium), a neurotoxin that harms dopaminergic cells in the brain (Langston *et al.*, 1983). This finding raised the possibility that PD could be triggered by environmental toxins. Later studies connected pesticides, such as paraquat as well as rotenone, to an augmented menace of PD, as they also suppress mitochondrial Complex-I and damage dopaminergic cells (Di Monte *et al.*, 1986). Further research has investigated potential connections between PD and factors such as cultivating, well spring, pastoral living, welding, and vulnerability to leaden metals, though the exact relationships remain unclear (Elbaz *et al.*, 2009).

Genetics

Although PD is primarily idiopathic, 10-15% of cases have a family history, and about 5% exhibit Mendelian inheritance patterns (Deng *et al.*, 2018). The risk of PD is also influenced by polygenic factors, which are not yet fully understood. So far, 23 PARK genes have been associated with PD, with modifications in these genes displaying either non-gonosomal presiding inheritance (e.g., SCNA, LRRK2) or autosomal recessive inheritance (e.g., PRKN, PINK1) (Gasser, 2011).

Classification of Anti-Parkinson drugs (KD Tripathi pharmacology book, n.d.)

Anti-parkinsonian drugs are divided into two classifications. Firstly, drugs influencing brain dopaminergic system.

- Dopamine precursor: Levodopa.
- Dopaminergic agonist: Bromocriptine, Ropinirole, Pramipexole.
- Peripheral decarboxylase inhibitors: Carbidopa, Benserazide.
- Monoamine oxidase-B (MAO-B) inhibitors: Seligiline, Rasagiline.
- Catechol-O Methyltransferase inhibitors (COMT): Entacapone, Tolcapone.
- Glutamate agonist (N-methyl-D-aspartate receptor) (Dopamine facilitator): Amantadine.
- Secondly, drugs affecting brain cholinergic system.
- Central anticholinergics: Trihexyphenidyl, Procyclidine, Biperiden.
- Antihistamines: Orphenadrine, Promethazine.

Available anti-parkinsonian drugs in the market and their dosage form

Levodopa is available as a single active pharmaceutical ingredient or in combinations with other anti-parkinsonian drugs like: Carbidopa, Benserazide etc. Some available dosage forms include tablets/capsules, Immediate-Release (IR) tablets, disintegrating tablets, Controlled Release (CR) tablets, Extended-Release (ER) capsules, intranasal and intravenous administration of drugs, oral inhalation, infusion through nasojejunal tube.

Levodopa novelty

Over the years, scientists and pharmacists have worked hand in hand to improve the bioavailability of levodopa by modifying the route of administration, incorporation of carriers, and altering the approach of preparations. These novelties have caused tremendous alteration in the bioavailability of levodopa. Some novelties on levodopa are discussed here.

Levodopa has been incorporated into different novel drug delivery systems like nanocarriers (Van Vliet *et al.*, 2023a), liposomes and micro particles, etc., (N. Ngwuluka *et al.*, 2010). These are done to upgrade the bioavailability of levodopa, additionally, enabling a more precise and prolonged release, which may minimize fluctuations and adverse effects (N. Ngwuluka *et al.*, 2010). These formulations are combined with neuro protective agents like antioxidants or neutrophilic constituent to slowdown the progression of neuronal deterioration in PD while maintaining indicator control (Herrero *et al.*, 2011). These discoveries has been studied for different deliveries like nasal deliveries (Simões *et al.*, 2020), subcutaneous delivery (for the 006 study group *et al.*, 2021), intra duodenal, etc., (Chang *et al.*, 2016).

Combination therapies, such as levodopa combined with COMT inhibitors (e.g. entacapone) or MAO-B inhibitors (e.g. rasagiline), have become standard for improving levodopa's effectiveness (Poewe and Antonini, 2015). These is done to prolong the effect of levodopa and improve its efficacy in treating PD symptoms (Poewe and Antonini, 2015).

Levodopa has also been used for gene-editing techniques like CRISPR-Cas9 to potentially correct genetic mutations related to PD and improve the way levodopa is utilized by the brain (Fiandaca *et al.*, 2020). It is also explored to deliver genes that could stimulate the production of dopamine or other neuroprotective factors in the brain. This could help reduce reliance on levodopa over time and improve its long-term efficacy (Nutt *et al.*, 2020).

Recent studies are focusing on distinguishing biomarkers that could predict how adeptly a patient will respond to levodopa (Titova and Chaudhuri, 2017), also aids in detecting and supporting the early diagnosis of PD (Frequin *et al.*, 2023). The goal is to provide a treatment avenue tailored to the individual. By using these biomarkers to adjust the dosage or type of remedy used. (e.g. dopamine transporter imaging), clinicians are aiming to tailor levodopa therapy based on individual patient characteristics (Yamashita *et al.*, 2023).

Though still in experimental stages, there is growing interest in combining levodopa with stem cell therapies which could help regenerate dopaminergic neurons, potentially providing long-term benefits and addressing the underlying

neurodegeneration in PD, while levodopa manages symptoms in the interim (Liu and Cheung, 2020). And, Deep Brain Stimulation (DBS) is an important adjunct therapy for advanced Parkinson's patients who do not respond well to medication alone. Research is ongoing to combine DBS with levodopa therapy to optimize the therapeutic effects and reduce the necessary dosage of levodopa, minimizing side effects (Lin *et al*., 2022).

The gut microbiome is also a novel way for management of PD. Studies has shown how gut bacteria may affect the absorption of levodopa and its effectiveness. Recent research has explored the role of gut-derived metabolites in the effectiveness of levodopa (Menozzi and Schapira, 2024). Since levodopa is primarily absorbed in the gut, certain microbial communities in the gastrointestinal tract may affect its bioavailability. Studies are investigating how altering the gut microbiome or metabolite levels may enhance the absorption and effectiveness of levodopa (Cheng *et al*., 2024).

Apart from levodopa being used for the treatment of Parkinson, Research is also being carried out to see how levodopa therapy impacts non-motor symptoms such as depression, cognitive decline, and sleep disturbances (Pantcheva *et al*., 2015). Studies are evaluating whether levodopa can be used not just to treat motor symptoms but also improve non-motor symptoms. This approach could potentially minimize the cognitive and psychological burden of Parkinson's which in turn enhancing the motor benefits of levodopa (Mazzucchi *et al*., 2015).

Functional imaging, such as Magnetic Resonance Imaging and Positron Emission Tomography scans, is being used to understand how levodopa affects brain activity in real time. This research is exploring whether levodopa therapy can improve the brain's ability to compensate for lost dopaminergic function, potentially leading to better symptom management (Niethammer *et al*., 2012). Some studies are exploring Virtual Reality (VR) as an adjunctive therapy to help patients with PD improve motor function, cognition, and gait. The idea is to combine VR-based rehabilitation with levodopa to boost its effects and potentially reduce the dose needed to achieve optimal symptom control (Samuel *et al*., 2017).

As the field of immunotherapy expands, there is growing interest in combining levodopa with immunotherapy strategies aimed at reducing inflammation in the brain. These therapies could help slow the progression of Parkinson's while improving the efficacy of levodopa in managing motor symptoms (Duwa *et al*., 2021).

Micro emulsions are colloidal systems that enhances the solvability and bioavailability of poorly water-soluble drugs like levodopa. These formulations are being investigated to intensify the absorption rate of levodopa, particularly in patients with gastrointestinal absorption issues, ensuring a more efficient and controlled delivery (Zainol *et al*., 2012).

Over the year's levodopa has been formulated into different types of formulations like: ER formulation, buccal tablets, transmucosal or sublingual formulation, transdermal patch e.t.c. All these formulations of levodopa are being improved to provide a sustained release of the drug over time. These formulations are designed to reduce motor inconstancy by maintaining a stable blood level of levodopa throughout the day (Nyholm, 2006). They bypass gastrointestinal tract and liver metabolism, allowing for faster onset of action and lessen fluctuations in plasma drug levels**.** It also helps to improve patient convenience (Espay *et al*., 2017).

Transdermal systems are being developed as a means of providing continuous levodopa release via the skin. This avoids gastrointestinal issues and provides a more stable delivery profile, reducing peak-to-trough fluctuations in plasma drug levels (Ghodke *et al*., 2024). Another novel drug delivery system involves using an intestinal patch designed to release levodopa directly into the gastrointestinal tract, ensuring uninterrupted and controlled drug release (Freitas *et al*., 2016).

The Duodopa system, which involves the unceasing infusion of levodopa-carbidopa gel directly into the duodenum, is especially useful for advanced PD. It provides constant levodopa delivery, significantly reducing motor fluctuations and improving "off" time (Shackleford *et al*., 2022).

Novel delivery systems and *in vitro* studies with levodopa

In vitro release kinetics of levodopa is a scientific experiment that takes place outside of a living organism. Nanoparticles has been used as a novel drug delivery system to achieve prolonged release of drug, refine the bioavailability, and also for CR (Van Vliet *et al*., 2023b). Some examples of nanoparticles include: Biodegradable nanoparticles, Solid Lipid Nanoparticles (SLNs). The *in vitro* release kinetics are crucial for understanding the drug's performance before clinical applications (Mogharbel *et al*., 2022). Research have shown that the release kinetics of levodopa from nanoparticles often follows Higuchi's model**,** zero-order kinetics, and first-order kinetics, indicating a diffusion-controlled mechanism. These nanoparticles have been shown to enhance the bioavailability of levodopa by protecting the drug and providing sustained release (Satapathy *et al*., 2021).

Liposomes, Microparticles (Vasa *et al*., 2017), and Microspheres are widely used for their capability to envelop drugs and provide regulated and prolonged release (S. Chen *et al*., 2024). Liposomal formulations enhance levodopa's bioavailability, and prolong its therapeutic effects. *In vitro* release studies shows that levodopa which is released from liposomal delivery systems typically follows diffusion-CR kinetics (García Esteban *et al*., 2018). Microparticles is used to improve the pharmacokinetic profile of levodopa by controlling the release over a prolonged period (Dankyi *et al*., 2020). *In vitro* release studies of levodopa from

microparticles shows that drug release follows first-order kinetics or Higuchi's model, thereby inferring the dispensing system is diffusion-controlled (Bahrainian *et al.*, 2021). Microspheres are often used for controlled drug release (Arıca *et al.*, 2005). They provide a sustained release profile and are commonly evaluated in *in vitro* release studies to assess the release kinetics (Mohanraj *et al.*, 2013).

Polymeric films can be used for CR of levodopa, especially for topical or transdermal delivery. *In vitro* release studies from these films are important to determine the release rate and ensure a consistent drug delivery profile (McAlister *et al.*, 2021).

Tablets has been modified over the years to different forms like gastric floating tablets which are created to remain in the gut for extended periods, providing prolonged drug release. Levodopa-loaded floating tablets are typically tested for *in vitro* release to determine the release profile under stomachic conditions ('Formulation and Evaluation of Levodopa Floating Tablet for Prolonged Gastric Retention and Sustained Release for the Management of Parkinson's Disease', 2024). These studies have shown CR of levodopa, with release kinetics that can be described by the Peppas model**,** which is often used for systems where anomalous transport occurs. Levodopa release kinetics from floating tablets often follow zero-order kinetics, indicating a constant release rate over time (Zhao *et al.*, 2025). Dual-release mode, combining both immediate and sustained release, are explored for levodopa to address both the immediate needs during the "off" period and the prolonged effects during the "on" period. These systems generally show a biphasic release pattern in which the IR phase is followed by a CR phase, typically governed by Higuchi diffusion (C. Chen *et al.*, 2012).

Hydrophilic matrices, Hydrogels are used as conveyors for levodopa. Levodopa release is controlled by allowing liquid to penetrate the matrix and gradually release the drug. In *in vitro* studies**,** levodopa release from hydrophilic matrices showed that the drug follows zero-order kinetics, where the drug is released at a continuous rate over time (N. C. Ngwuluka *et al.*, 2015). Hydrogels are often used for sustained drug delivery, particularly for conventional or topical administration (K *et al.*, 2024). Levodopa-loaded hydrogel systems are evaluated for their release profiles in *in vitro* conditions (Michalicha *et al.*, 2023).

Dual-release systems, are explored for levodopa to address both the immediate needs during the "off" period and the prolonged effects during the "on" period (Dingemanse *et al.*, 1998). These systems generally show a biphasic release pattern in which the IR phase is followed by a CR phase, typically governed by Higuchi diffusion (Descombes *et al.*, 2001)**.**

Polymeric micelles, nanogels and nanoemulsions are another promising delivery system for levodopa, providing an improved solubility profile for poorly soluble drugs. *In vitro* release studies of levodopa from these systems generally indicate CR over extended periods, and the release kinetics are often described by the Korsmeyer-Peppas model**,** indicative of non-Fickian diffusion (Y. Zhang *et al.*, 2021). Studies on levodopa-loaded nanoemulsions have demonstrated that the release of the drug follows Higuchi diffusion model or first-order kinetics, depending on the composition of the nanoemulsion (Nirale *et al.*, 2020).

Natural biopolymers like chitosan and alginate have been used to develop levodopa-loaded systems that allow CR (Tan *et al.*, 2018). *In vitro* studies have shown that levodopa release from these biopolymers can be controlled through ionic gelation and diffusion mechanisms. It also helps to determine how these formulations behave in biologically relevant media. The release kinetics of such formulations often follow the Higuchi model or Peppas-Korsmeyer model (Q. Zhang *et al.*, 2012).

Biodegradable polymers have been used in levodopa delivery systems to achieve sustained release. These polymers degrade over time, releasing levodopa in a controlled manner. *In vitro* studies show that levodopa release follows zero-order kinetics up to a certain concentration, then transitions to first-order release as the polymer degrades (Alabrahim and Azzazy, 2022).

Preclinical studies

Study of levodopa using pig model was undertaken to provide insight into *in vivo* performances of two gastroretentive systems (*PXLNET* and IPB matrices) in comparison to Madopar Hydrodynamically Balanced System capsules. The pig model was used to assess gastric residence time and pharmacokinetic parameters using blood, Cerebrospinal Fluid (CSF), and urine samples. Histopathology and cytotoxicity testing were also undertaken. The pharmacokinetic parameters indicated that levodopa was liberated from the drug delivery systems, absorbed, widely distributed, metabolized, and excreted (N. C. Ngwuluka *et al.*, 2017).

In vivo studies were conducted in rat model using intranasal gel for the determination of percentage amount of levodopa in brain following the intranasal administration of all the formulation. The drug was estimated in rat brain excised after intranasal administration of the formulations at regular intervals in different groups of rats. Concentration of levodopa in brain homogenate was estimated by spectroscopic method using standard curve in rat brain homogenate. The pharmacokinetic parameters indicated that the rise in uptake of levodopa was seen following intranasal route compared to oral route of administration (Sharma *et al.*, 2014).

In vivo study using rat substantia nigra and striatum was done to determine the consequences of acute and chronic administrations of 1-Benzyl-1,2,3,4-tetrahydroisoquinoline on the effects of L-DOPA in the rat brain using behavioural and biochemical assays. L-DOPA (100 mg/kg i.p.) produced a significant increase in the horizontal locomotor activity of rats (Wąsik *et al.*, 2014).

A study on the regulating effects of (-)-Epigallocatechin-3-Gallate (EGCG) on L-DOPA methylation along with its impact on chemically induced oxidative neuronal damage and degeneration in rats reported that EGCG strongly inhibits human liver COMT mediated O-methylation of L-DOPA in a concentration-dependent manner (Nagai *et al*., 2004). Oral administration of EGCG moderately lowered the accumulation of 3-O-methyldopa in the plasma and striatum of rats treated with L-DOPA + carbidopa. Furthermore, EGCG also diminished glutamate-induced oxidative cytotoxicity in cultured HT22 mouse hippocampal neuronal cells by deactivating the nuclear factor κB-signaling pathway. *In vivo*, administration of EGCG demonstrated a powerful protective effect against kainic acid-induced oxidative neuronal death in the hippocampus of rats (Nadler *et al*., 1980). These findings proposed that oral administration of EGCG could provide considerable benefits for Parkinson's patients receiving L-DOPA and carbidopa offering mild inhibition of L-DOPA methylation alongside potent neuroprotection against oxidative damage and degeneration (Kang *et al*., 2010).

In vivo evaluation of Levodopa-loaded nanoparticles for nose to brain delivery in mice compared oral levodopa versus intranasal levodopa versus Levodopa-loaded nanoparticle (intranasal) to find out which is more effective. Blood and brain tissues were used to check the dopamine level. Locomotor activity as well as spontaneous activity was determined. Oral levodopa showed 1.17% brain uptake, Intranasal levodopa showed 35.6% brain uptake and Levodopa-loaded nanoparticle following intranasal route showed an average of 76.8% in brain uptake (Arisoy *et al*., 2020).

A series of polymeric nanocarrier systems was reported using Poly (Lactic-co-Glycolic Acid) (PLGA) and chitosan for L-Dopa. Efficient absorption of the drug through the nasal epithelium, with rapid entry into the CNS, while avoiding first-pass metabolism when tested on male Wister rats was achieved. The positive charge on the nanoparticles facilitates their transport across the nasal epithelium by increasing their retention time in the nasal cavity. This extended retention time is likely due to electrostatic interactions between the nanoparticles and the negatively charged sialic acid residues found on the mucus in the nasal linings (Migliore *et al*., 2010). The Area Under the Curve (AUC) for L-Dopa-loaded chitosan nanoparticles was notably double that of L-Dopa drug solution administered intranasally. Additionally, L-Dopa absorption was significantly improved-about twofold-when delivered as chitosan nanoparticles, comparison to the unaltered L-Dopa. The findings indicate that encapsulating L-Dopa in chitosan nanoparticles for intranasal delivery might be a promising strategy to improve the drug's bioavailability in PD treatment (Ahmad *et al*., 2022).

Continuous transdermal delivery of levodopa based on a self-assembling nanomicellar system in rabbits demonstrated that transdermal administration offers a continuous, CR, providing steady dopaminergic stimulation and reducing motor fluctuations while oral administration of levodopa leads to quick elimination, leading to fluctuations in blood concentration that may cause motor issues and dyskinesia. The researchers explored transdermal L-DOPA delivery using a self-assembling nano-micellar system containing 2% L-DOPA and 1% carbidopa. *In vitro* and *in vivo* studies in rabbits showed significantly improved absorption and permeation of L-DOPA. This method suggests that a once or twice daily regimen could effectively manage symptoms, depending on disease severity (Sintov *et al*., 2017).

A new bilayer tablet was designed with IR layer containing nebicapone and a sustained release matrix layer incorporating Levodopa and Carbidopa (LCN PR tablets). Pharmacokinetic study in Gottingen minipigs revealed that levodopa concentration reached their peak later with the LCN PR tablets compared to Sinemet. Nebicapone boosted the maximum plasma concentration and AUC of levodopa. These findings suggest that LCN PR tablets could reduce the number of tablets and daily doses for Parkinson's treatment (Sousa E Silva *et al*., 2011).

Levodopa requires continuous administration to the upper intestine to maintain therapeutic levels, which can be realized with a Controlled Release Gastroretentive Dosage Form

Table 1: Epidemiology of PD (Connolly and Lang, 2014).

Epidemiological Features	Details
Mean age of onset	60
Men: Women	1.5:1
Incidence, per 1000 person-years	
Patients aged 55 - 65 years	0.3
Patients ≥85 years	4.4
Prevalence, %	
Total population	0.3
Patients >60 y	1
Idiopathic: hereditary, %	90:10
Life expectancy	Varies with age of onset and occurrence of dementia
Clinical subgroups, %	
Tremor-dominant	8
Akinetic-rigid	26
Mixed	66
PD protective factors	Cigarette smoking, high coffee consumption
PD contraindication	Family history of the disease, pesticide exposure, head injury, constipation.

N/B: Constipation may be an early symptom rather than a risk factor.

(CR-GRDF). This study developed a novel CR-GRDF using unfolding polymeric membranes with high rigidity and extended dimensions. The pharmacokinetics of levodopa in CR-GRDFs were tested in beagle dogs pre-treated with carbidopa. The optimized CR-GRDF maintained therapeutic levels of levodopa for 9 hr, significantly extending absorption time compared to non-gastroretentive CR-particles and oral solution. This CR-GRDF can enhance levodopa therapy and may be applied to other drugs with narrow absorption windows (Klausner *et al*., 2003).

To assess the total bioavailability of oral levodopa, plasma concentrations and urinary excretion of levodopa and its metabolites were determined in beagle dogs and in Parkinson's patients following intravenous and oral drug administration of commercial levodopa preparations. The absolute bioavailability of orally administered levodopa was estimated to be about 35% in both dogs and patients; however, the total amount absorbed of intact drug and levodopa metabolites was estimated to be 80-90% of the administered dose. Due to the similarities of the pharmacokinetic characteristics of levodopa found in beagle dogs and in humans, beagle dogs can serve as a model to study bioavailability, absorption, and metabolic mechanisms (Sasahara *et al*., 1980).

A study investigated how inhibiting skin sphingosine synthesis enhances the permeation of Levodopa (LD) across rat skin. Beta-chloroalanine (beta-CA), a serine palmitoyl transferase inhibitor, was used to block sphingosine synthesis. Treatment with beta-CA significantly reduced sphingosine levels in perturbed skin. LD permeated better across beta-CA-treated skin, suggesting that lower sphingosine content enhances LD permeation. A single topical application of carbidopa-LD to treated skin resulted in higher C_{max}, faster T_{max}, and sustained plasma levels of LD for 28 hr. These results show that inhibiting sphingosine synthesis can improve systemic LD delivery (Gupta and Tiwary, 2002).

A new lipophilic L-Dopa derivative, L-dopa-butylester, was synthesized to enhance transdermal delivery. In an *in vivo* study, an L-dopa-butylester sheet was applied to shaved rat skin with a hydrogel containing L-menthol and ethanol. Plasma levels of L-Dopa rose steadily within 30-180 min, while L-dopa-butylester was not detected. L-dopa levels were higher than when L-Dopa was applied alone. These results suggest that L-dopa-butylester enhances skin penetration and is quickly converted to L-Dopa in the body (Sudo *et al*., 2002).

A new two-layer system was developed to maintain L-Dopa stability in hydrogel. L-dopa sheets were created by immersing L-Dopa solution in wiper sheets and lyophilizing them. In a rat cutaneous absorption study, the L-Dopa sheet was applied to shaved skin with a hydrogel containing absorption enhancers. L-dopa effectively penetrated the skin, and plasma levels peaked after application. This system preserved L-Dopa stability while ensuring effective transdermal absorption (Iwase *et al*., 2000).

Clinical trials involving levodopa (ongoing and completed)

In a clinical trial preladenant was assessed as an adjunct to levodopa in patients with PD and motor fluctuations. Preladenant is a powerful and selective A_{2A} antagonist. In rodent and primate models of PD, preladenant enhanced motor function (Hodgson *et al*., 2010). In a Phase 2b trial testing preladenant as an add-on to levodopa in patients with PD (Hauser *et al*., 2011), a dose response was observed with preladenant (5 mg and 10 mg twice daily) resulting in a significant decrease in off time compared to placebo, and preladenant was well tolerated (Hauser *et al*., 2015).

Dyskinesia is one of the most challenging symptoms in advanced PD. Around 50% of patients experience dyskinesia four to five years after treatment starts and about 90% after nine years (Van Laar, 2003). Dyskinesia is believed to result from intermittent stimulation of postsynaptic dopaminergic receptors due to multiple oral levodopa doses. In cases of severe neurodegeneration, erratic absorption, unpredictable gastric emptying, and the short half-life of levodopa, frequent oral dosing can lead to unstable levodopa concentrations in the bloodstream, causing fluctuating dopamine levels in the basal ganglia (Antonini *et al*., 2010). To address this issue, Levodopa-Carbidopa Intestinal Gel (LCIG) is used. This formulation is continuously administered to the upper intestine via percutaneous endoscopic gastrostomy with J-tube extension using an external pump (Nyholm *et al*., 2003). LCIG provides more consistent levodopa plasma levels compared to traditional oral levodopa therapy, reducing the likelihood of motor complications and dyskinesia (Nyholm *et al*., 2005).

A study compared the Pharmacokinetics (PK) of a 24-hr continuous subcutaneous infusion of foslevodopa/foscarbidopa with the LD pharmacokinetics from 16-hr LCIG, followed by night-time oral LD/Carbidopa (CD) doses. The LD exposure following subcutaneous infusion of foslevodopa/foscarbidopa (Rosebraugh *et al*., 2021) over 24 h were similar to those of LCIG LD/CD administered over 16 hr followed by two oral doses at 18 and 21 hr after the start of LCIG delivery. Therefore, foslevodopa/foscarbidopa subcutaneous infusion provides levodopa exposures comparable to LCIG throughout the day (Rosebraugh *et al*., 2022).

In a double-blind, double-dummy, double-titration Phase 3 trial in advanced PD patients, the efficacy and safety of LCIG infusion were characterized relative to IR oral Levodopa-Carbidopa (LC-oral) treatment (Othman and Dutta, 2014). The outcomes of this study clearly demonstrate that LCIG results in lower variability and fluctuations in levodopa and carbidopa plasma concentrations compared to LC-oral (Othman *et al*., 2015a). The enhanced pharmacokinetic profiles of LCIG were in line with its

superior efficacy compared to oral levodopa, as shown in this study (Othman *et al*., 2017).

A trial was conducted to compare the efficacy of jejunal infusion of LCIG versus oral administration of levodopa-carbidopa tablets for treating advanced PD. Ethnic differences in the response to levodopa-carbidopa therapy and oral dosing requirements have been suggested. Asian patients with PD appear to need 20-30% lower oral levodopa doses to manage their symptoms and seem to develop dyskinesia more often than Caucasians (Wood and Zhou, 1991). This results in higher levodopa bioavailability or greater pharmacodynamic sensitivity in Japanese individuals. LCIG led to a more favourable pharmacokinetic profile, which was linked to a reduction in motor complications compared to oral levodopa (Othman *et al*., 2015b).

IPX203 is a novel oral ER formulation of Carbidopa (CD) and Levodopa (LD) designed to address the short half-life and limited absorption area of LD in the gastrointestinal tract. IPX203 is an innovative drug created using advanced technology, containing IR granules and ER beads, which allows for rapid LD absorption to reach the desired plasma concentration and maintain it within the therapeutic range longer than current oral LD formulations (Modi *et al*., 2019). Administration of IPX203 with a high-fat, high-calorie breakfast delayed the initial rise in LD concentration by approximately 2 hr and increased C_{max} and AUC_{tau} by 20% compared to the fasted state in a Phase 2, open-label, rater-blinded, multicenter, crossover study in patients with advanced PD (LeWitt *et al*., 2023).

Opicapone is a novel, once-daily, potent third-generation catechol-O-methyltransferase inhibitor. Aimed at evaluating the safety and efficacy of opicapone as an adjunct to levodopa compared to placebo or entacapone in patients with PD and motor fluctuations. Opicapone (BIA 9-1067) is a hydrophilic 1,2,4-oxadiazole analogue with a pyridine N-oxide residue at position three offering strong COMT inhibitory potency without causing cellular toxicity (Kiss *et al*., 2010). Opicapone has a high binding affinity (Nuno Palma *et al*., 2012), which results in a slow dissociation rate and long-lasting effect, enabling once-daily dosing. It also reduces COMT activity, increases systemic levodopa exposure, and improves motor response compared to placebo. which translates into a slow complex dissociation rate, and long-lasting effect enabling once-daily dosing compared to placebo (Ferreira *et al*., 2015; Ferreira *et al*., 2016).

CONCLUSION

Parkinson's disease remains a complex and progressive neurodegenerative disorder with significant challenges in its management. Despite levodopa being the gold standard for treatment, long-term administration is associated with complications, necessitating innovative approaches to enhance its efficacy and minimize side effects. Advances in drug delivery systems, combination therapies, gene-editing techniques, and gut microbiome research offer promising avenues for improving levodopa bioavailability and therapeutic outcomes.

The integration of alternative administration routes, such as intranasal delivery and transdermal systems, has demonstrated potential in increasing levodopa absorption and reducing fluctuations in plasma drug levels. Furthermore, emerging strategies like deep brain stimulation, immunotherapy, and virtual reality-based rehabilitation present novel adjunctive therapies that could complement levodopa treatment and enhance patient quality of life. Functional imaging studies continue to provide insights into PD progression and levodopa's impact on brain activity, paving the way for more personalized treatment approaches.

Future research should focus on refining these innovative strategies, optimizing levodopa formulations, and exploring neuroprotective interventions to slow disease progression. With ongoing advancements in biotechnology and pharmacology, there is hope for more effective and individualized treatments that can significantly improve the management and prognosis of Parkinson's disease.

ACKNOWLEDGEMENT

The authors are thankful to Rajiv Ghandi University of Health Sciences, Bangalore for access to research journals and to Nargund College of Pharmacy, Bangalore for computer systems and internet facility.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AUC: Area under the curve; **CNS:** Central nervous system; **CR:** Controlled release; **DALY:** Disability-adjusted life years; **DBS:** Deep brain stimulation; **ER:** Extended-release; **IR:** Immediate-release; **LC:** Levodopa-carbidopa; **LCIG:** Levodopa-carbidopa intestinal gel; **PD:** Parkinson's disease; **PEGJ:** Percutaneous endoscopic gastrostomy with J-tube; **SANS:** Self-assembling Nano-micellar system; **SLN:** Solid lipid nanoparticles; **VR:** Virtual reality.

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Cite this article: Mercy OI, Devi VK, Joshi VG, Nayak GD, Urmila GH, Nidhi M, Priyanka N. Anti-Parkinson Drug Levodopa: It's Novel Delivery Systems, Preclinical and Clinical Studies: A Review. Int. J. Pharm. Investigation. 2026;16(1):1-11.