CURRENT ADVANCES IN THE TREATMENT OF PARKINSON'S DISEASE BASED ON NANOTECHNOLOGY

Abstract

Parkinson's Disease (PD), the fastest growing brain disorder, the most prevalent movement disorder, and the second most prevalent neurodegenerative disease affecting the world. The current available treatment strategy for PD focuses to raise dopamine levels and is focused on the motor complications and could only provide symptomatic relief. None of the anti-parkinsonian therapies, alone or in combination are capable to halt PD and the associated neurodegeneration on a long-term basis. Thus, several researchers based on new drug delivery system with the aim to achieve brain specific delivery and to reduce the limitations of the current therapies have been developed. Amongst which nanotechnology approaches has gained fame in the management of various neurological disorders including PD. This chapter highlights the up-to-date advances of nano-based therapeutic strategies for the effective management of PD.

Keywords: Parkinson's disease; Neurodegeneration; Nanotechnology; Central Nervous system; Brain specific delivery

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I. INTRODUCTION

The "shaking palsy" now referred to as Parkinson's disease (PD), was first described clinically by English physician Dr. James Parkinson in 1817 [1]. PD, a progressive neurological disorder primarily associated with older people is the second most prevalent neurodegenerative disease affecting the world [2,3]. PD is recognised as hereditary and sporadic PD. The sporadic PD are reported to be more complex which makes up to 90% of all the total cases [4]. Earlier, PD was mostly thought as a movement disorder with a tetrad of motor impairments, such as idle tremor, rigid muscles, slowed movement, and loss of balance. Nevertheless, now PD is known as a multi-system condition with considerable immunological dysfunction and neuroinflammation, which is associated with the onset of other non-motor symptoms, including sleep and gastrointestinal disorders that can appear long before a patient is diagnosed [5]. In PD, dopamine-producing neurons in the substantia nigra of the brain that helps to control movement undergo degeneration [6,7]. In recent years, PD has been one of the world's fastest-growing neurological disorders [8]. Unlike other neurological disorders, the incidence of disability and mortality from PD is increasing faster. Approximately 8.5 million people had PD in the 2019 global estimation [9]. This disease affects 1%- 2% of the population for those aged >65 years [10]. Deaths from Parkinson's significantly increased from 1994 to 2019 [11]. Furthermore, the entire population of people affected by PD is expected to surpass 12 million by 2040 unless novel therapies are developed to halt, slow down, or prevent the disease's progression [12].

The death of a particular group of neurons, the dopaminergic neurons, that send axons to the striatum, is thought to be responsible for the loss of several crucial motor features [13,14]. Due to this, the majority of modern pharmacological therapy methods for PD attempt to improve striatal dopaminergic tone [15,16]. Currently approved drugs for treating PD are dopamine replacement strategies using the dopamine precursor Levodopa (L- DOPA) [17]. Despite offering symptomatic relief, none of the drugs has been shown to slow down or prevent the disease's progression [18]. Furthermore, the clinical efficacy of L- DOPA therapy gradually decreases as the disease progresses, with the onset of further complications associated with long-term L- DOPA therapy such as wearing off and dyskinesias [19,20,21]. Moreover, dopamine delivery to extrastriatal regions, fluctuations in absorption and travel through the blood-brain barrier (BBB), continuous non-physiological dopamine production, and its impact on dopamine receptors in the basal ganglia all contribute to the fact that current treatments, while often successful at enhancing motor function, are also linked with significant side effects [22,23]. This necessitates the development of new therapeutic approaches that could effectively manage PD.

Several researchers have developed novel drug delivery systems (NDDS) to achieve brain-specific delivery and reduce the limitations of current treatment. Among these, nanotechnology approaches have gained fame in managing PD with increased bioavailability and excellent stability [24]. Some of the NDDS that are being explored in managing PD are liposomes, solid lipid nanoparticles (SLNs), nanoemulsion, self-emulsifying drug delivery systems (SEDDS), and niosomes [25]. In this context, this chapter will focus on the present advancement of nano-based therapeutic strategies in the management of PD highlighting its composition, advantages as well as nanomaterials.

II. INSIGHTS OF NANOTECHNOLOGY IN PD

The production of nanoscale materials falls under the interdisciplinary fields of nanotechnology and nanoscience. Richard Feynman first lay out to the idea of miniaturization and the underlying principles of these fields in his legendary talk, "There's Plenty of Room at the Bottom," which was given 50 years ago [26]. While nanotechnology attempts to use these altered materials for the layout, assessment, and forged a better structure, and systems with controlled size and shape (1-100 nm) for numerous uses, nanoscience is primarily focused on manipulating materials at the atomic or subatomic level whose properties differ significantly from those of bulk matter. A description of a nanomaterial for nanomedicine includes a variety of submicron-sized materials in addition to those with a size beneath 100 nm. The important part is to take advantage of the submicron-sized materials' size-dependent change in characteristics, which can be used to influence cellular responses. Nanostructures have been used in medical imaging, therapies, drug delivery, reconstruction of tissues, and disease diagnosis. The manipulation of diverse systems at the nanoscale enabled by nanotechnology has the potential to improve PD treatment by achieving continuous drug release and reducing the drug toxicity [26,27]

III. VARIOUS NANOMATERIALS USED IN NANOTECHNOLOGY

Nanomaterials are the fundamental components of nanotechnology. A nanomaterial has at least one dimension that is smaller than 100 nm (nanoscale). Four distinct kinds of nanomaterials are distinguished based on their dimensionalities [28].

1. **Zero-Dimensional Nanomaterials (0-D):** At the nanoscale, these materials show all three of their dimensions. E.g.: The fullerene molecule, nanoparticles, and quantum dots [28].

2. **One-Dimensional Nanomaterials (1-D):** 10^9 represents the one billionth unit of production of one-dimensional nanomaterials, used in various scientific disciplines, with thicknesses ranging from 1 nm to 100 nm. The fabrication of electronics, storage systems, nanometre LEDs, optoelectronic, chemical-based, the detection of bios magneto optics, fibre optic systems, and optical devices makes extensive use of these nanomaterials. Important materials at the nanoscale, among them nanotubes, double-walled nanotubes, nanobelts, nanowires, nanoribbons, and hierarchical nanostructures, are constructed using one-dimensional nanomaterial (15). E.g.: Nanotubes, nanofibers, nanorods, nanowires, and nanohorns [28].

3. **Two-Dimensional Nanomaterials (2-D):** Key components of nanodevices are constructed from 2D nanomaterials, which have two dimensions and a distinctive shape that are outside the range of nanometric size. Nanoreactors, sensor photocatalysts, nanocontainers, nanocontainers, and templates for 2D structures are all examples of two-dimension nanomaterial uses. E.g.: Nanosheets, nanoflims, and nanolayers [28].

4. **Three-Dimensional Nanomaterials (3-D) or Bulk Nanomaterials:** The key characteristics influencing the use and efficacy of nanostructures are shape, size, and morphology, which govern how nanomaterials behave. Over the past ten years, interest in three-dimensional nanomaterials has grown in medical science and research. Numerous applications for these nanoparticles exist in the fields of catalysis, batteries, and reactant- and

product-transport by magnetic materials [28].E.g.: Fullerenes, Dendrimers, and Quantum dots.

Overall, the nanoparticles have their specific composition in their structures. Table 1 depicts the different nanoparticles formulations with its characteristics and advantages

Table 1: Various nano-formulations with its characteristics and advantages

Type	Structures	Characteristics	Advantages	References
Polymer based	Polymeric nanoparticles /nanospheres	Tiny pieces of matter; they exhibit nanocapsule / nanosphere characteristics.	The structure of a nanosphere resembles a matrix, whereas that of a nanocapsule is core-shell.	33
	Polymeric micelles	Amphiphilic copolymer solutions, hydrophobic core and aqueous shell configurations. typically PEGs)	Hydrophilic shell may inhibit RES uptake since it can solubilize medicines that aren't water soluble. Improve the bioavailability and reliability of drugs. The micelle shell prevents the drug's interaction with non-target cells and serum proteins	29, 30
	Dendrimers	Complex 3-D structure with intrinsic antiaggregation properties.	Dendrimers promote the endocytosis-mediated cellular internalisation of medicines across a variety of cell membranes or biological barriers.	29,30
Lipid based	SLNs	In aqueous environments, SLNs are made up of a lipidic core made of solid lipids at room temperature that is encircled by a surfactant layer; Solid biodegradable fats	Environmentally friendly; There is no usage of organic solvents;manufacturing method that is repeatable and scalable.	29, 34
	Nanostructured Lipid Carriers (NLC)	The lipidic component is made up of a combination of liquid and solid lipids.	High entrapment effectiveness; Weak drug ejection	34
	Nanoemulsions	Oil, water, and an emulsifier combine to generate nanoemulsions, which have droplet sizes between 20 and 500 nm.	Decreased first-pass metabolism; Particles with larger surfaces dissolve more quickly and start acting more quickly.	29, 34
	Liposomes/ micelles	A phospholipid bilayer and an internal aqueous area make up the vesicular systems	Enable high-efficiency hydrophobic and hydrophilic drug encapsulation in liposomes for sustained release,	29,34

			improved intracellular transport, reduced toxicity, and widespread therapeutic application.	
	Exosomes	Generated from cells	Minimal immunogenicity, good biocompatibility, low toxicity, cross-BBB crossing, and high drug loading efficiency.	29
Others	Carbon nanotubes (CNTs)	Helical nanostructures made of carbon comprising a few layers; they can be single-wall or multiwall CNTs; Multiple sizes and shapes, a sizable usable surface area	The development of nanotube-neural hybrid networks can enhance synapse development, network connectivity, and neuronal activity.	29, 30
	Graphene	carbon atoms bound together in a hexagonal honeycomb; strong mechanical durability, enhanced stretch, superior thermal conductivity, and optical characteristics	Biological samples including glucose, hemoglobin, cholesterol, dopamine, and uric acid can all be identified with it	31
	Fullerene	Nanomaterial with hollow cage shape, single or multilayer.	electron affinity, structure, flexibility, and electrical conductivity.	32
	Metal nanoparticle	Due to impact on resonance characteristics, they have special optoelectrical capabilities aluminum, gold, iron, lead, silver are well-known metal nanoparticles.	Superparamagnetic characteristics of iron, size-dependent electrochemistry with gold, good penetration, inert, non-immunogenic, facile synthesis in a range of geometries, easy surface modification	29,32

IV. NANOTECHNOLOGY BASED TREATMENT USED IN PD

Dopamine is currently replaced with an exterior supply of dopamine, such as L-DOPA, in the treatment of PD. Yet the prolonged side effects of this medication can cause motor difficulties [35]. Continuous activation of dopaminergic neurons, however, may result in improved tolerance with few adverse effects. Therefore, fresh approaches are needed to extend the course of treatment and ensure that medications release gradually over time [36]. The inability to get across the BBB is the fundamental hurdle to effectively treating PD. Only low molecular weight and high lipophilic molecules can readily cross from the blood into the brain [37]. Drug molecules can be adapted to cross the BBB and enter the CNS. Numerous experiments with particle sizes ranging from 10 to 400 nm have been conducted in the last few years to investigate these innovative drug delivery methods. Because of advances in nanotechnology, Novel Drug Delivery Systems (NDDS) are frequently used as drug carriers

to transport medications across biological barriers, including the BBB of the CNS. These are incredibly sophisticated systems that have many advantages over traditional dosing forms [38]. Optimization of the dosage, lower production costs, patient compliance, targeted and controlled drug distribution, a longer duration, and fewer side effects are some of these [37]. Metallic nanoparticles, liposomes, nanoemulsions, dendrimers, carbon nanotubes, and micelles are examples of such systems [38]. They are designed in such a way that they can supply a suitable amount of medication to the brain. SLNs, which are likely to serve as drug carriers for the regulated and targeted delivery of medications to the CNS, have contributed to yet another advancement in the field of nanotechnology.

1. **Liposome:** Due to their many benefits over alternative delivery systems, liposomes have attracted a lot of attention as innovative vehicles for enclosing diverse pharmacologically active substances. They can encapsulate both lyophilic and lyophobic medications, which is a unique ability. They are also biocompatible, biodegradable, have fewer adverse effects, don't trigger the immune system, and deliver pharmaceuticals to specified sites [39, 40]. In recent years, liposomal formulations for a variety of CNS-active medications have been created in orderto provide a prolonged release impact by raising the L-DOPA concentration in thenigrostriatal system through more efficient transport. Numerous studies have demonstrated the use of different liposomes for the treatment of PD. Unilamellar liposomes were used to encapsulate and deliver a number of L-DOPA dimeric prodrugs intraperitoneally. These formulations showed an increase in baseline dopamine levels and a protracted release of dopamine in the central nervous system. Table 2 lists different liposomal formulations utilized for the PD management.

Table 2: Various Liposomal formulation studied in PD

Sl. No.	Drug	MOA	Reference
1	Levodopa (ClTx-LS)	↑ drug uptake ↑ dopamine and DAA level in substantia nigra ↓ behavioural diseases ↓ TH dopaminergic neuron degeneration	Xiang *et al*., 2012
2	Curcumin	↑ motor behaviour; obstructed neuronal cell death ↓ apoptotic index neither catalepsy nor dyskinesia are present.	Chiu *et al*., 2013
3	Dopamine	↑ PD treatment outcomes ↓ PD complications	Lopalco *et al*., 2018
4	Resveratrol	↑Effectiveness and durability in encapsulation ↑ prolonged drug release ↑ concentration in the brain	Wang *et al*., 2018

2. **Solid Lipid Nanoparticles (SLNs):** For the treatment of numerous neurological illnesses throughout the past few years, SLNs have proven to be a potent vehicle for the regulated administration of CNS-active medications [41]. The SLN formulations consist of two or more surfactants and/or co-surfactants, as well as a mixture of lipids having a low melting

point. A few examples of lipids are monostearin, stearyl alcohol, stearic acid, glycerol monostearate, Precirol® ATO5, Compritol® 888 ATO, and cetyl palmitate. Poloxamer 188, Tween® 80, and dimethyl dioctadecyl ammonium bromide (DDAB) are three common surfactants [42]. SLN has several advantages over other formulations, including effectiveness, targeted and controlled drug release, improved stability, decreased toxicity, and biodegradability. Drug delivery by topical, oral, ocular, and parenteral routes has been studied for SLNs. They are frequently employed for encapsulating medications to treat PD due to their particular benefits over delivery systems. Table 3 lists the several SLN formulations that are used to treat PD.

Table 3: Various SLNs formulation studied in PD

Sl. No.	Drug	MOA	Reference
1	Apomorphine (SLN)	↑ oral bioavailability ↑ brain striatum targeting ↑ ability to treat PD	Tsai Ming-Jun *et al.,* 2011
2	Bromocriptine	↑ half-life of the drug	Esposito *et al.,* 2008
3	Idebenone	↑ IDE penetration into biological membranes ↑ bioavailability ↑ antioxidant activity	Montenegro *et al.,* 2011
4	Riluzole	↑ efficacy ↑ ability to cross BBB ↓ systemic toxicity	Bondì *et al.,* 2010
5	Ropinirole	↑ Drug permeation ↑ Sustained release ↓ reduction in tremors ↑ therapeutic efficacy	Pardeshi *et al.,* 2013
6	Coumarin	Sustained release effect, ↑cellular uptake in Caco 2 cell lines, ↑ permeability in brain microvascular endothelial cell line (hCMEC/D3 cells)	Fernandes *et al.,* 2018

3. **Nanoemulsions:** Nanoemulsions are formulations with submicron dimensions that are kinetically and thermodynamically stable. Essentially, they are stabilized oil-in-water emulsions made with emulsifiers such surfactants and co-surfactants. These are given in droplets with modest dimensions between 20 and 200 nm and a large surface area [43]. In order to effectively treat CNS illnesses, the BBB must be crossed and the medicine must reach the brain. Only medications that are very lipid-soluble can successfully penetrate the BBB. Because of their potential advantages over alternative delivery systems, such as amplified drug loading, improved drug solubility in water, increased bioavailability, controlled release, prevention against chemical or enzymatic degradation, along with the quick onset of action, nanoemulsions are increasingly used today for effective drug delivery to the CNS [44,45]. To deliver medications directly to the brain and prevent first-pass metabolism, the nasal route is used [46]. The several nanoemulsion formulations studied in PD are listed in Table 4 below.

Table 4: Various nanoemulsion formulations studied in PD.

Sl. No.	Drug	MOA	Reference
1	Naringenin	↑ GSH and SOD level ↓MDA level	Gaba *et al*., 2019
2	Schisantherin A	↑Bioavailability	Fei Sa *et al*., 2015
3	Selegiline	↑ drug uptake ↑bioavailability ↑antioxidant deficits and dopamine level	Kumar *et al.,* 2018
4	Resveratrol +Cur-cumin	↑ brain targeting of thepolyphenols ↑ solubility ↑ stability	Nasr M, 2016
5	Resveratrol	↑ drug conc in brain ↑ GSH and SOD level ↓ degenerative changes ↓ MDA level	Pangeni *et al*., 2014
6	Ropinirole	↑ bioavailability ↑ conc in brain	Mustafa *et al*., 2012
7	CoEnzyme Q10	↑ behavioural activity ↑glutathione level ↓dopamine depletion ↓ thiobarbituric acid reactivesubstances	Gupta *et al*., 2018

4. **Niosomes:** The creation of niosomes, which have a bilayer structure and appear to be promising NDDS, often involves the interaction of a non-ionic surfactant and cholesterol. They are widely utilized to improve solubility and stability and enable controlled release delivery to specific sites [47]. Their size, makeup, numberof lamellae, and surface charge are all adaptable, allowing for optimization to change their performance as needed. The effective administration of several pharmacological drugs in numerous kinds of sick states is made possible by the widespread use of niosomes. Niosomes have a lot of benefits, including being non-immunogenic, biocompatible, and degradable, which makes them an exciting possibility for CNS drug delivery [48]. Table 5 shows various niosomal formulations studied in PD.

Table 5.: Various niosomal formulations studied in PD

Sl. No.	Drug	MOA	Reference
1	Pramipexole-encap-sulated,PEGylate	↑ relative fluorescenceintensity ↑ efficacy in 6-OHDA-lesioned rats ↓ dose reduction	Gunay *et al.* 2017
3	Bromocriptinemesy-late	↑ Drug permeation(3.2 times) ↓ cataleptic behavior	Vavia *et al.* 2018

2	Pentamidine	↑ CNS localization ↑ stability ↓ toxicity ↓ cost	Rinaldi F *et al.* 2019

5. **Polymeric Nanoparticles:** Polymeric nanoparticles (NPs) have a matrix system which is composed of natural and synthetic polymers. They are highly biocompatible, biodegradable, and are non-toxic. There are two forms of polymeric NPs: nanospheres and nanocapsules. In nanospheres, the drug is evenly diffused in a matrix system, whereas in nanocapsules, the drug is enclosed in a cavity and the cavity is enclosed by a polymeric membrane [49]. The use of polymeric NPs as drug carriers has several advantages, including the potential for controlled or sustained drug delivery systems [50], also improve bioavailability and therapeutic index [51].

Table 6. Various polymer-based formulations studied in PD

Sl. No.	Drug	MOA	Reference
1	Lactoferrin (Lf)	↑ brain bioavailability ↑ accumulation of drug in the cortex, substantia nigra and striatum region, substantially reduced the 6-OHDA-induced striatum damage	Hu *et al.* (2011)
2	Levodopa (LD)	↑ brain uptake, avoid degradation of LD in peripheral circulation	Sharma *et al.* (2013)
3	Bromocriptine (BRC)	↑ uptake of drug into the brain	S. Md *et al* (2013)
4	Ropinirole hydrochloride (RH)	↑ uptake of drug into the brain, ↑brain bioavailability improved mucoadhesion of the drug	Jafarieh *et al.* (2014)

The most common FDA-approved synthetic polymers to prepare nanoparticles for pharmaceutical application include polylactic acid (PLA), poly lactic-*co*-glycolic acid (PLGA), and poly (ethylene glycol) (PEG) [52]. Among the natural polymers the most commonly used polymer is chitosan. Chitin deacetylation produces chitosan, a natural biopolymer. It has been recognised as a flexible polymer for the development of delivery systems due to its biocompatibility, high charge density, non-toxicity, and mucoadhesion [53]. The numerous polymer-based formulations examined in PD are shown in Table 6.

6. **Microsphere and Microcapsules:** The term "microencapsulation" refers to the engineering of particles with a size between 1 and 1000 nm [54] in which a solid or liquid medicine is enclosed, resulting in a polymer shell called microcapsule or dispersed in a polymeric matrix called microsphere. Microspheres were initially used in the 1960s. Microspheres are a control release system that has obtained FDA approval. Unlike other methods of drug delivery, microspheres have some significant benefits, such as (i) The abili-

ty to alter the materials and fabrication techniques to regulate the rate and duration of drug release; (ii) improved stability in comparison to alternative controlled-release systems; (iii) improved patient compliance as a result of patients needing fewer doses more frequently [55]. Chitosan, alginate, and collagen are just a few examples of natural sources that can be used to synthesize several polymers for microencapsulation. Other materials include PCL (polycaprolactone), PLA (polylactic acid), and D,L-PLGA (a co-polymer composed of lactic and glycolic acids).[56] Among all the polymers, D,L-PLGA has been extensively used for the production of parenteral microspheres due to its biocompatibility and biodegradability [57]. Several techniques are being studied for drug delivery across the BBB. For example, the implantation of microspheres directly into the brain can restrict the systemic toxicity of integrated medications and determine the therapeutic drug concentration in the given area [58]. Table 7 shows various microsphere formulations studied in PD.

Table 7: Various microsphere formulations studied in PD

Sl. No	Drug	MOA	Citation
1	Pramipexole	drug release up to 2 weeks	Li *et al.*, 2019
2	Rasagiline	In-vitro sustained release up to 45 days after single-dose administration, enhanced pharmacodynamics for up to 30 days	Kanwar *et al.,* 2019
3	L-DOPA, CD	Over 90% drugs released within 24 hours.	Parthipan *et al.*, 2018
4	Ropinirole	50% drug released in 12 hours via zero-order kinetics.	Kashif *et al.,* 2016
5	Glial cell line-derived neurotrophic factor (GDNF)	Single dose increased motor function and restored dopaminergic function.	Garbayo *et al.,* 2016
6	GDNF	GDNF released from microsphere for 25 days in in-vitro tests.	Agbay *et al.*, 2014

7. **Self-Emulsifying Drug Delivery Systems (SEDDS):** Lipid-based formulations have been getting a lot of attention lately, with an aim to ameliorate the oral bioavailability of lipophilic drugs by the use of SEDDS [59]. They are an isotropic mixture of natural or synthetic oils, solid or liquid surfactants, co-solvents/ surfactants. The ability of the emulsion to self-emulsify is mainly determined by the polarity of the emulsion, the size and charge of the droplets, the concentration of the surfactant, and the oil/surfactant ratio [60]. Therefore, it is crucial to take specified excipient combinations into account in order to develop effective self-emulsifying systems. The key benefit of SEDDS is that the medi-

cine stays dispersed throughout the GI tract [61]. Table 8 shows various SEDDS studied in PD.

Table 8: Various SEDDS formulations studied in PD

Sl. No.	Drug	MOA	Reference
1	CoEnzyme Q10	↑ Bioavailability ↑ Absorption ↑neuroprotective effect	Balakrishnan *et al.* (2009)
2	Entacapone	↑ Shelf life ↑ Patient compliance ↓ TBARS & nitrate levels ↑Glutathione and catalase levels	Vadlamudi *et al.* (2016)
3	Rutin	↑ Bioavailability (2-3 times) ↑Glutathione	Sharma *et al.* (2016)
4	Bromocriptine mesylate	↑ Bioavailability ↑ Aqs solubility ↑Stability ↑ Dissolution behaviour	Hussein *et al.* (2018)

V. CONCLUSION

Nanotechnologies are emerging as potential treatments for neurological disorders, including PD. They could make it possible to create drug delivery systems with a variety of properties. It is an excellent substitute for treating PD since it significantly improves transporting across the BBB, drug absorption and permits targeted drug administration. Numerous anti-parkinsonian medications, including L-DOPA, curcumin, idebenone, and others, are considerably enhanced by the use of nanocarriers. However, there are still concerns regarding toxicity and NP biocompatibility. More research is required to ensure safe clinical use.

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