INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Nanotechnology In Parkinson's Disease

Mihir Parmar[2], Dev Gandhi[2], Deep Parekh[2], Hunedali Tinwala[2], Taufik Mulla[1]*

[1]Assistant Professor, Department of Pharmaceutics, Krishna School of Pharmacy & Research, A Constituent School of Drs. Kiran & Pallavi Patel Global University, Varnama, Vadodara, Gujarat, India.
[2]B.Pharm Student, Krishna School of Pharmacy & Research, A Constituent School of Drs. Kiran & Pallavi Patel Global University, Varnama, Vadodara, Gujarat, India.

ARTICLE INFO

Received: 20 March 2024
Accepted: 24 March 2024
Published: 02 April 2024
Keywords:
Nanotechnology, Parkinson's disease, Drug delivery, Neurodegeneration
DOI:
10.5281/zenodo.10953569

ABSTRACT

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons, leading to motor and non-motor impairments. Despite extensive research, current therapeutic strategies face challenges such as limited blood-brain barrier permeability, off-target effects, and inadequate bioavailability. Nanotechnology emerges as a promising avenue to address these limitations and revolutionize PD treatment. This review article systematically explores the recent advancements in applying nanotechnology for the diagnosis, treatment, and understanding of Parkinson's disease. Nanoparticles, including liposomes, polymeric micelles, and dendrimers, exhibit unique properties that enhance drug delivery, improve bioavailability, and enable targeted release within the brain. Moreover, multifunctional nanocarriers allow for simultaneous diagnosis and therapy, facilitating personalized and precise treatment approaches. The integration of nanomaterials in imaging techniques provides unprecedented insights into the pathological progression of PD, aiding early diagnosis and intervention. Furthermore, nanoscale platforms offer potential for gene therapy, neuroprotective agents, and modulation of inflammatory responses, presenting a multifaceted approach towards halting disease progression. As we delve into the intricate interplay between nanotechnology and Parkinson's disease, this review discusses the challenges, ethical considerations, and future prospects associated with the translation of these innovative technologies into clinical practice. By harnessing the power of nanotechnology, this comprehensive overview aims to inspire further research and development, fostering a new era of effective, targeted, and personalized therapies for Parkinson's disease.

INTRODUCTION

Background of Parkinson's Disease

***Corresponding Author:** Taufik Mulla
Address: *Assistant Professor, Department of Pharmaceutics, Krishna School of Pharmacy & Research, A Constituent School of Drs. Kiran & Pallavi Patel Global University, Varnama, Vadodara, Gujarat, India.*
Email : mullataufik@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Neurodegenerative diseases place significant demands on the public and health sectors due to the immune system's subsequent activation of the central nervous system (CNS). Immune activation can cause neurodegeneration, ischemia, infections, and immune-mediated disorders, but it can also help with regeneration and repair through a variety of other mechanisms like limiting neurotropic viral infections and eliminating necrotic cells. Close to 0.3% of the world's population is estimated to have Parkinson's disease (PD), with a crude incidence rate of 4.5–19 cases per 1,000 people annually. The World Health Organization estimated that in 2005, there were 1,617,000 disability-adjusted life years (DALYs) lost globally as a result of Parkinson's disease (PD). By 2030, that number is expected to rise to 2,015,000 years. [1, 2, 3] Although there are traces of Parkinsonism in previous diagnoses, James Parkinson's 1817 medical definition of Parkinson's disease was initially given as a neurological illness. Even older, mentions of Parkinson's disease can be found in ancient Chinese and traditional Indian scriptures dating back to about 1000 BC. Parkinson presented six case drawings, three of which included patients that were spotted in London's streets and one that was only seen from afar. When Jean-Martin Charcot returned to the Salpeterre more than 50 years later, he was more detailed in his explanations and identified bradykinesia as a distinct characteristic of the disease.Because he understood that people with Parkinson's disease are not always trembling or noticeably weak, Charcot was also the first to propose the term "Parkinson's disease," replacing the previous classification of paralysis agitans or shaking palsy. In his "Manual of Diseases of the Nervous System," London-based William Gowers provided a significant analysis of the demography of Parkinson's disease by detailing his own observations with eighty patients in the 1880s. He observed the disease's characteristic joint abnormalities and accurately determined that the condition had a small male predominance. Most of the additional clinical reports and research on the pathologic alterations associated with Parkinson's disease came from the French neurologic school. The clinical and morphologic characteristics of the increasing phases of Parkinsonian impairment were described by Richer and Meige (1895). Babinski made a point regarding the peculiar motor fluctuations that are inherent in the illness. Brissaud was the first to postulate that Parkinson's disease originated from injury to the substantia nigra. During the 1920s, Treitiakoff, Foix, and Nicolesco investigated the disease's connection to more pathologic examinations of the midbrain. Greenfield and Bosanquet carried out the most thorough pathologic investigation of Parkinson's disease and the precise demarcation of the brain stem lesions in 1953.In a seminal work that initially presented their now-internationally recognized staging approach, Hoehn and Yahr examined the morbidity and clinical course of Parkinson. The foundation of this established staging approach is the differentiation between unilateral disease (Stage I) and bilateral disease (Stages II–V), with the emergence of postural reflex impairment (Stage III) marking a significant shift in the disease's clinical relevance.[4]

Nanotechnology in medicine

When drugs, heat, light, or other substances are delivered to particular cells in the human body for the purpose of detecting and treating diseases or injuries within those targeted cells, as little harm as possible is done to the body's healthy cells. This technique is known as nanomedicine. Using nanotechnology to improve human health and well-being is known as nanomedicine. One billionth of a meter is called a nanometer. Though it is hard to fathom anything so tiny, consider something that is just 1/80,000th the breadth of a human hair. The width of a red blood cell is roughly 7000 nm. Deoxyribonucleic acid (DNA),

the genetic material, is made up of four nucleotide bases with sizes varying from sub-nanometers to nanometers. The diameter of DNA's double helix structure is also in the nanometer range. These materials and devices can be engineered to interact with cells and tissues at a molecular (i.e., subcellular) level with a high degree of functional specificity for applications to medicine and physiology. This allows for a level of technological and biological system integration that was previously unattainable. It should be understood that nanotechnology is not a single, new scientific field in and of itself, but rather the result of the convergence of several traditional sciences, including biology, chemistry, physics, and materials science, in order to gather the necessary collective expertise for the development of these cutting-edge technologies.[5,6,7,8] Novel drug delivery methods that use highly porous self-assembling bilayer tubule systems or nanoparticles—particularly for the blood brain barrier in certain cases—are an example of such an application. Chemically functionalized dendrimers, highly branched molecules with a "tree-like" branching structure, are another class of applications being investigated. These molecules can be utilized as contrast agents for magnetic resonance imaging (MRI) or as molecular building blocks for gene therapy agents. [10,9]

Significance of Nano solutions in Parkinson's Care

A new, efficient, and cutting-edge approach to getting neurotherapeutics over the blood-brain barrier is nanotechnology. Over the past few decades, the use of nanomedicines in CNS drug delivery has shown great promise because of their ability to utilize surface-tailored biocompatible and biodegradable nanomaterials, as well as their unique physicochemical properties and nanosized range. Nanotechnology may be used to tailor the site-specific transport of medications, along with other substances, across the blood-brain barrier. This technology can fulfill specific functions as needed. The drug, which is part of the nanoengineered complex along with other necessary functions, is the pharmacologically active part that needs to be administered. For instance, it can encapsulate the active ingredient, shield it from enzymatic breakdown, release it at a specific pH, cross the blood-brain barrier, and target particular brain cells. [12,13]

Stimulus responsive nanoparticles

Recent advances have led to the development of nanoscale biomedical imaging for image guided therapy and neurodegenerative disease diagnostics. Magnetic nanoparticles (MNPs) with MRI contrast are one of the most researched multipurpose systems for applications such as drug administration, tissue healing, hyperthermia, and cellular and molecular imaging of different metastases. Structural barriers, such as the blood brain barrier, limit the ability of MNPs to enter the central nervous system in cases of neurodegenerative disorders. Consequently, it's critical to carefully design MNPs with the right size and physicochemical characteristics in order to go past the BBB and into the brain. Target-specific theranostics was recently created by Qiao et al. (2012) to help nanoparticles traverse the blood-brain barrier via endocytosis mediated by the lactoferrin receptor. Lactoferrin-modified PEGylated magnetic nanoparticles (Fe3O4) are used as a brain MRI guided delivery probe. Amphiphilic PEG coating and lactoferrin conjugation promote MNP transport across the blood-brain barrier, according to an in vitro model of the pig BBB. Following targeted MNP injection intravenously, vascular imaging confirms that lactoferrin receptor-mediated transcytosis occurs when targeted nanoparticles engage with lactoferrin receptors expressed on microvascular endothelial cells. Hwang et al. (2009) have documented the use of ultrasound responsive stable perfluorocarbon nanobubbles (PNs) loaded

with apomorphine, a dopamine receptor agonist, to target specific brain regions. According to the investigations, the stiff cholesterol and phospholipid membrane of apomorphine-loaded PNs in vivo contributed to their increased stability and longer plasma residence duration. On demand, the release profiles were modified by ultrasound trigger. The safety profile of PNs (<10% hemolysis) was confirmed by an erythrocyte hemolysis study [100]. The combined results of these investigations demonstrated the promise of stimulus-sensitive nano-carriers for enhancing the stability, frequency of administration, and on-demand release kinetics of PD therapies.[14]

UNDERSTANDING PARKINSON'S DISEASE

Parkinson's disease (PD) is regarded globally as a second chronic neurodegenerative ailment that occurs often. Dopamine levels in the striatum are lowered in Parkinson's disease (PD) due to the degeneration of dopaminergic neurons in the substantia nigra region of the brain.[15]

Symptoms

Before the cardinal motor characteristics of Parkinson's disease (PD) manifest, up to 80% of dopaminergic cells in the nigro-striatal pathway are thought to be destroyed. Usually, the earliest motor symptoms of the condition lead to a diagnosis. Bradykinesia is the slow start of voluntary movements accompanied by a progressive decrease in the amplitude and speed of repeating activities; it may also include muscle rigidity, resting tremor, or postural instability. Most of the time, one side of the body experiences symptoms first, and a few years later, the other side experiences symptoms as well. The propensity toward a shuffling gait, axial and limb rigidity with or without the cogwheel phenomenon, stooped posture, and lack of arm movement during walking are all present. Bradykinesia can result in hypomimia, or an expressionless face, and micrographia, or reduced handwriting amplitudes. Approximately 80% of people exhibit limb tremor, most frequently a resting pill-rolling hand tremor. The propensity of the thumb and index finger to make contact and move in a circular motion is associated with the phenomenon known as "pill rolling." Other tremor kinds may also appear, and the tremor occasionally affects the legs. Oral motor disorder is widespread. More than half of the patients experience speech disorders, such as rushed and extremely quiet speaking; 40–80% of the patients report swallowing difficulties; and 25% of the patients report dribbling saliva.[16]

Another motor PD sign is dystonia. A prolonged muscular contraction that frequently coexists with atypical postures, motions, or both is referred to as dystonia. Though dystonic symptoms in Parkinson's disease (PD) are primarily associated with treatment—medical and surgical—this may infrequently be a prediagnostic symptom. Prediagnostic dystonias that are commonly observed include unilateral equinovarus foot posture, flexion of the forearm or upper arm, writer's cramp, oro-mandibular dystonia, torticollis, or various combinations of these symptoms. Most of the time, PD symptoms start to show up ten years after the dystonia first manifests. Dystonia in juvenile onset familial Parkinson's disease (PD) usually affects the foot, causing pain akin to cramps or inversion of the affected foot.[17]

The non-motor symptoms of Parkinson's disease

Patients may experience a range of pre-motor symptoms prior to the onset of motor symptoms and the diagnosis being established. These could begin ten or more years before the diagnosis is made, and presenting with symptoms other than motor ones could cause the diagnosis to be delayed. A study involving 109 patients who had just received a diagnosis but had not yet begun treatment revealed that symptoms like constipation, excessive daytime sleepiness, lack of

emotional involvement and interest (apathy), and sleep issues could occur in as many as 60–70% of patients before the diagnosis and were more common than in normal controls. Anxiety and depression can also manifest long before a diagnosis is confirmed. Pre-motor symptoms differ from patient to patient, but they always persist even when further motor or non-motor Parkinson's disease symptoms may emerge along the course of the disease. As the illness progresses, patients typically experience non-motor symptoms to be more bothersome than motor symptoms. Here, the non-motor symptoms are divided into four categories: sensory symptoms, sleep disturbances, cognitive and mental disturbances, and autonomic function disturbances.[18]

Disturbances in autonomic function

Autonomic dysfunction might occur before a diagnosis is made, show symptoms as the illness worsens, or be brought on by medicine. The central and peripheral postgan-glionic autonomic nerve systems are both thought to be involved in autonomic dysfunction. Thirty to forty percent of patients have orthostatic hypotension. This is characterized as a decrease of > 20 mm Hg in the systolic blood pressure or > 10 mm Hg in the diastolic blood pressure after standing or tilting head-up to at least 60 degrees in less than three minutes. When the body is in an upright position, hypotension-induced hypoperfusion of the brain can cause lightheadedness, blurred vision, and cognitive impairment, which may occur before unconsciousness. Symptoms related to the stomach are frequent. Although symptoms like postprandial fullness and gastric retention indicate a slowing of the gastrointestinal tract's motility, slow-transit constipation accounts for 70–80% of cases. Patients with dysfunctional rectal sphincters may also have trouble emptying their bladders. Incontinence, urgency, and frequency of urination are examples of abnormalities in urinary control. Sixty percent of patients report frequent nocturia, which is brought on by overactive detrusor muscles. In guys, erectile dysfunction is prevalent.[19]

Sleep disturbances

Anatomical structures and central neurotransmitters involved in the regulation of the physiological sleep cycle are known to be impacted by the neuropathology of Parkinson's disease (PD). Research using polysomnography has revealed alterations in the structure of sleep waves when compared to healthy controls; however, medication used to treat certain Parkinson's disease symptoms may also cause disruptions in sleep at night. Most people sleep in fractions. According to sleep studies, patients tend to wake up during the night more frequently and to sleep shallower. Fractionated sleep may also be caused by other Parkinson's disease symptoms as depression, nocturnal tremor, frequent nocturia, and difficulty turning over in bed. Up to 50% of people are thought to experience excessive daytime sleepiness, which may be partially brought on by dopaminergic medications. Similar to PD, sleep syndromes are more prevalent in controls. Up to 50% of people are thought to experience excessive daytime sleepiness, which may be partially brought on by dopaminergic medications. Similar to PD, sleep syndromes are more prevalent in controls. Patients are more likely than controls to experience the symptom of restless legs, with or without periodic leg movements during sleep.[20]

Diagnosis

One of the difficulties with Parkinson's disease (PD) is that its indications and symptoms are frequently subtle. If doctors are not actively looking for these symptoms and indicators, they may only consider a PD diagnosis in the event that more noticeable discoveries are made. The UK PD Brain Bank criteria bases the diagnosis of Parkinson's disease (PD) on three phases. First, if bradykinesia coexists with another primary

symptom, such as rigidity, tremor, or postural instability, Parkinson's disease (PD) can be diagnosed. Second, it is necessary to review the exclusion standards. A history of multiple head injuries, encephalitis, neuroleptic treatment, toxins such as manganese, carbon monoxide, cerebral tumors, communicating hydrocephalus on CT scans, strictly unilateral features after three years, and typical features of atypical Parkinson's disease (PD) such as cerebellar, pyramidal, or oculomotor symptoms are typical examples. The determination of supportive criteria for Parkinson's disease (PD) is the third step. PD is supported by a number of factors, including severe levodopa-induced dyskinesia, excellent responsiveness to levodopa, unilateral onset and persistent asymmetry, and disease progression.[21] Primarily 76% of individuals with Parkinson's disease (PD) have Lewy bodies, if clinical examination is the primary diagnostic method used. For example, postural instability is not a very helpful clinical symptom when the disease is first developing and the diagnosis is not yet confirmed. Before the patient reaches Hoehn and Yahr (HY) stage 3, which is an advanced stage, this symptom does not appear [4]. As such, postural instability is not a useful diagnostic tool for children. In fact, current therapy may even delay the onset of HY stage 3, meaning that other symptoms may prove to be more diagnostically useful. The presence of resting tremor, reduced arm swing, muscle soreness, and slower repetitive motions is used to make the initial clinical diagnosis of Parkinson's disease (PD).

Tremor

Most of the time, unilateral resting tremor (HY stage 1) originates in the upper extremities. After then, it either spreads to the ipsilateral lower limb or to the opposite upper limb. Elderly people may come with less complaints of tremor than younger ones, but their gait abnormalities may be more pronounced. Age does not seem to have an impact on akinesia or stiffness. Since many individuals with "mixed" tremor may go on to acquire an apparently more benign variety of PD, the link between essential tremor (ET) with action tremor and PD with resting tremor is not straightforward. According to PET studies, bradykinesia and rigidity are more closely associated with the reduction in dopamine production than tremor is. DaT SPECT imaging was licensed by the US Food and Drug Administration (FDA) in 2011 to differentiate essential tremor from Parkinson disease; however, routine scans are not required for this purpose.[22]

Bradykinesia

It is best to avoid using the term "akinesia" because most patients with Parkinson's disease are not truly akinetic, at least not in the early stages of the disease. Bradykinesia is the term used to describe the most prevalent clinical sign of Parkinson's disease (PD): slowness of speed. Clinical manifestations of bradykinesia include difficulties writing and cutting food, hypo-mimia, which is typically more noticeable on one side of the face, and restricted arm swing on one side, which is frequently misdiagnosed by patients and doctors as an orthopedic issue. [23]

Rigidity

It is best to test for stiffness using erratic motions to prevent the patient from resisting or facilitating the test. Cogwheel rigidity is a common occurrence in advanced stages of Parkinson's disease (PD). When unsure whether rigidity is present, the Froment maneuver should be used; this involves moving one limb voluntarily while the researcher looks for an increase in muscle tone in the other limb. When individuals with ET also exhibit the cog-wheeling phenomena, which is brought on by sporadic increases in tremor, confusion and uncertainty arise.[24]

Postural Instability

Postural instability is not a particularly helpful cardinal sign in the early stages of Parkinson's

disease (PD), as was previously mentioned, because this symptom does not develop before to HY stage 3. When doing the pull test, the examiner should teach the patient to resist a rapid pull or, if required, rectify the behavior. On average, five years after Parkinson's disease (PD) onset, postural instability manifests. Further supporting our belief that this so-called cardinal sign is misleading is the fact that up to 70% of the elderly have compromised postural reflexes.[25]

Methods

The Parkinson Study Group created the double-blind Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) trial to assess the effects of selegiline hydrochloride, vitamin E, both medications taken together, and placebo on the disease's course. The trial was subsequently modified to enable a systematic 7.6-year follow-up of the subjects. To put it briefly, 28 US and Canadian hospitals enrolled 800 individuals with early Parkinson's disease (PD) (Hoehn and Yahr stages 1 and 2). 528 (66%) men and 272 (34%) women made up the 800 patients.

Patients

Only patients between the ages of 30 and 79 who the investigators believed had idiopathic PD, modest disability, and symptoms for five years or fewer were considered candidates for the trial, even though the diagnostic criteria of PD were not defined. The study excluded participants who had resting tremor (≥3 on the Unified Parkinson's Disease Rating Scale), depression (16 on the Hamilton Psychiatric Rating Scale), or dementia (22 on the Mini-Mental State Examination).The following standards are derived from the typical case report forms that are filled out at yearly follow-up exams: Four factors indicate that the investigator is not more than 40% confident in the diagnosis of Parkinson's disease (PD); (2) PD is not one of the three most likely diagnoses that the investigator has listed; (3) the features or course of the illness is not thought to be typical for PD; and (4) there is significant autonomic dysfunction with a background of akinetic-rigid syndrome.

Statistical analysis

Using 2-tailed t tests and $\chi 2$ tests, the characteristics of patients at the DATATOP baseline visit were compared with patients thought to have (735) and not have (65) idiopathic PD. Using 2-tailed t tests, the duration of symptoms and length of follow-up for the 60 patients who were deemed to have an incorrect diagnosis of idiopathic PD based on clinical criteria (i.e., not by autopsy) were compared with the 735 patients with PD in order to mitigate the potential for bias resulting from different follow-up durations. The enrolling investigator was included as a stratification factor in this model, and treatment with selegiline at randomization was included as a covariate. From the Unified Parkinson's Disease Rating Scale, composite scores for bradykinesia, tremor, stiffness, postural instability, and gait impairment (PIGD) were obtained. The time-to-event analysis only included data from the initial DATATOP study, i.e., prior to all patients being transferred to selegiline medication.

Treatment

For decades, researchers have been working on therapeutic drugs with the goal of slowing the disease's rapid course. They simply address the symptoms and provide a limited amount of relief. These treatments have a number of negative side effects that get worse as the illness progresses. Most patients are administered dopaminergic medicines since the depletion of dopamine is the primary cause of most symptoms associated with Parkinson's disease. The goal of these drugs is to either restore the DA neurotransmitter or mimic its effects. As a result, they enhance the synchronization of muscular movement, which lowers the implicated muscles' rigidity and the frequency of tremors. The medicine levodopa (L-Dopa), a precursor to dopamine, is the gold standard for treating Parkinson's disease

symptoms.23,24 L-Dopa can cross the BBB and turn into DA, in contrast to DA. Since L-Dopa is susceptible to extensive peripheral metabolism once taken orally and cannot cross the blood-brain barrier (BBB), it is typically used in combination with benderizine or carbidopa (also known as DDC-I, or dopa decarboxylase inhibitors)25 to prevent the drug from decarboxylating into DA in the systemic circulation and maximize the amount of L-Dopa that reaches the central nervous system while minimizing side effects in the short term. But L-Dopa's broad peripheral metabolism results in a number of negative side effects, including nausea, drowsiness, and, most significantly, dyskinesia, particularly when taking the drug for an extended period of time. As a result, long-term L-Dopa plus DDC-I treatment for Parkinson's disease (PD) patients can eventually cause significant motor fluctuations, rendering this combination useless for ongoing dopaminergic stimulation.25 The disadvantages of oral L-Dopa are mitigated by oral inhalation L-Dopa, particularly peripheral L-Dopa decarboxylation. DA receptors are activated and release of DA when DA agonists act on them. Conversely, anticholinergics, like benztropine and trihexyphenidyl, cause the release of DA by activating DA receptors. While monoamine oxidase B (MAO-B) inhibitors largely limit the degradation of L-Dopa and DA in the brain, selective catechol-O-methyl transferase (COMT) inhibitors can predominantly suppress the peripheral degradation of the L-Dopa medication to boost the BAV of L-Dopa. In order to exercise their anti-parkinsonian effect, adenosine A2A receptor antagonists, such as istradefylline, can reduce the excessive inhibition of globus pallidus externus gab aminergic (GABAergic) neurons and the overactivity of striatopallidal neurons.[26]

Here are some of the various therapies used in the treatment of Parkinson's Disease:

Pharmacotherapy for Parkinson's Disease

Treatment options for Parkinson's disease (PD) symptoms include monotherapy for early-stage disease, combination therapy for advanced-stage disease, and combination therapy with different therapeutic agents of different categories for complex-stage disease. The first line of treatment for early Parkinson's disease (PD) may be monotherapy with monoamine oxidase (MAO-B) inhibitors, such as selegiline and rasagiline, if the patient has minor motor impairment but no cognitive impairment. Treatment for advanced Parkinson's disease (PD) can involve starting with DA agonists (ropinirole, rotigotine, pramipexole, apomorphine, bromocriptine, cabergoline, etc.) in addition to MAO-B inhibitors if the patient has mild to moderate motor dysfunction but no cognitive impairment. Treatment for complex Parkinson's disease (PD) involves combining levodopa, a DA precursor, with catechol-O-methyl transferase (COMT) inhibitors (entacapone, tolcapone, etc.) to treat moderate to severe motor impairment and cognitive impairment.[27] Their views indicate that these tactics either substitute essential enzymes for the manufacture of neurotransmitters to restore lost brain functions, or they use neurotrophic factors to increase the function of the diseased brain's surviving dopaminergic neurons.[28]

Cell therapy

Even though intrusive methods are often quite effective at treating symptoms, they rarely make a significant attempt to treat the disease's underlying cause. Therefore, the restorative methods for the dopaminergic nigrostriatal tract that involve cell treatment and neurotrophic support may be particularly useful. Over the last ten or so years, cell therapy has become a major treatment option for Parkinson's disease (PD) by replacing the nigronal striatum's degenerating or absent dopaminergic neurons.[29]

The Need For Innovative Approaches

As a multifactorial disorder, Parkinson's disease (PD) need a range of combination therapy in order to reduce symptoms and slow the disease's rapid progression. Even though L-Dopa has long been regarded as the gold standard treatment, some pre-existing symptoms may eventually deteriorate due to its low BAV and higher administration frequency. Another difficulty in treating PD patients is getting over the blood-brain barrier. Consequently, to enhance the administration of DA/L-Dopa in the CNS and improve results for PD patients, biocompatible delivery devices that can get beyond the aforementioned problems must be developed. In recent years, nano neurotechnology—more specifically, the use of nanotechnology for medication delivery in the treatment of NDs—has offered encouraging solutions to the associated problems .It is likely that numerous therapeutic techniques acting through distinct systems will need to be developed. For patients with PD, regardless of its severity or etiology, this would be the best course of care. Lessening the stigma attached to Parkinson's disease (PD) and improving patient education and comprehension will be possible via acceptance of the illness. Progress in the field would also benefit from the delivery of surface-engineered nanocarrier systems using active or passive targeted approaches. In conclusion, in addition to being approved by the pharmaceutical market, the nano-enabled system created for clinical applications for the treatment of Parkinson's disease (PD) ought to be commercialized on an industrial scale at reasonable costs. In order to draw a valid conclusion, we are hopeful that in the near future, drug delivery via nanotechnology based on nose to brain will play a significant role in the therapies provided to patients with Parkinson's disease.[30]

NANOTECHNOLOGY PRIMER

Basics of Nanotechnology

Above all, nanotechnology is a way of thinking. While the scientific community is enthralled by nanoscience, the majority of current debates, definitions, and attention are directed toward nanotechnology. The term "technology on the nanoscale" sums up nanotechnology the simplest. The ability to manipulate and reorganize matter at the atomic and molecular size, between about 1 and 100 nm, and to take use of the unique characteristics and phenomena at that scale in contrast to those linked to single atoms, molecules, or bulk behavior, is known as nanotechnology. The application of nanoscience, particularly to industrial and commercial goals, is known as nanotechnology. It is based on the manipulation, control, and integration of atoms and molecules to build material, structures, components, devices, and systems at the nanoscale. Innovative opportunities for the development of creative nanostructured materials and nanosystems are presented by the discovery of new materials, phenomena, and processes at the nanoscale as well as the advancement of unique theoretical and experimental research approaches. Regarding its applications in energy, electronics, medicine, agriculture, and other fields, nanoscale research and nanotechnology are projected to make numerous advances in the near future. The pace of these advancements is quickening. The application of nanoscience, particularly to industrial and commercial goals, is known as nanotechnology. It is based on the manipulation, control, and integration of atoms and molecules to build material, structures, components, devices, and systems at the nanoscale. Innovative opportunities for the development of creative nanostructured materials and nanosystems are presented by the discovery of new materials, phenomena, and processes at the nanoscale as well as the advancement of unique theoretical and experimental research approaches. Regarding its

applications in energy, electronics, medicine, agriculture, and other fields, nanoscale research and nanotechnology are projected to make numerous advances in the near future. The pace of these advancements is quickening..The National Science Foundation (NSF) financed a cross-disciplinary initiative called "Partnerships in Nanotechnology" from 1997 to 1998. The NSF had its first program focused on nanoparticles in 1991. However, it wasn't until 1998–2000 that the disparate domains of nanoscale engineering and science came together with a single, definition based on science and a 10-year research and development plan for nanotechnology. These were outlined in Nanotechnology Research Directions (Roco et al., 1999), a National Science Foundation workshop report that was officially endorsed by the National Science and Technology Council (NSTC) in 2000.These were the important strides that helped define nanotechnology as the 21st-century technology.After consulting with specialists from more than 20 nations, a definition of nanotechnology was decided upon in 1998–1999 (Siegel et al. 1999) and gained some level of worldwide recognition. The ability of scientists to reorganize matter at an intermediate length scale and the unique behavior of matter serve as the foundation for this definition.[31] The inventor of modern nanotechnology is physicist Richard Feynman, winner of the 1965 Nobel Prize in Physics. He first introduced the idea of atomic-level matter manipulation in a talk titled "There's Plenty of Room at the Bottom" at the 1959 American Physical Society meeting at Caltech. This innovative concept opened up new avenues for thought, and Feynman's theories have since been validated. He is regarded as the founding father of contemporary nanotechnology because of these factors. The term "nanotechnology" was first used by Japanese scientist Norio Taniguchi, over 15 years after Feynman's presentation, to characterize semiconductor processes that took place on the order of a nanometer. He argued that the processing, separation, consolidation, and deformation of materials by a single atom or molecule constituted nanotechnology. The 1980s marked the start of nanotechnology's golden age. When carbon nanotubes were created by Iijima, a fellow Japanese scientist, the field of nanotechnology moved even further.[32]

Applications in Medicine

Using nanotechnology to improve human health and well-being is known as nanomedicine. The field of nanotechnology and nanodrugs has yielded a large array of findings. Significant advancements in nanomedicine have raised the drug to a new level with important implications for healthcare. Research on the enormous potential of nanotechnology in healthcare is necessary. In the medical field, a great deal of research is being conducted on optimal techniques and approaches, such as nephrology, cardiovascular disease therapeutic genes, and cancer therapy. Newer medication delivery systems based on nanotechnology techniques are being tested for viral infections, fungal infections, cancer, diabetes, and gene therapy. The medication's targeting and improved safety profile are this therapy modality's key benefits. Moreover, magnetic nanoparticles, fluorescent dyes, and contrast agents made possible by nanotechnology are used in diagnostic medicine.[33]

Table 1 Nanoparticles used for medical applications

Study Phase	Product	Description	Use	Manufacture
Preclinical	MRX 952	Nanoparticle preparation to encapsulate camptothecin analogues	Tumors	IMA Rx Therapeutics

Preclinical	Targeted Nano Therapeutics (TNT)™ System	TNT with polymer coated iron oxide magnetic particle	solid tumors	Triton Biosystem
Preclinical	AuroLase™	Gold nanoshell	Head and neck cancer	Nano spectra Biosciences Inc
Preclinical	Dendrimer-Magnevist#	PAMAM dendrimer	MRI imaging agent	Dendritic Nanotechnologies Inc
Phase 1	VivaGel®	Dendrimer based microbicide gel	HIV prevention	Starpharma Pty Ltd
Phase 1	INGN 401	Nanoparticle formulation of tumor suppression gene FUS1	Lung cancer	Introgen Therapeutics Inc
Phase 1&2	Cyclosert-Campthothecin-IT 101	β-Cylcodextrin polymer drug delivery system	Solid tumors	Calando Pharmaceutics
Phase 2	VivaGel®	Dendrimer based microbicide gel	HSV prevention	Starpharma Pty Ltd
Phase 2	MRX 815	Nanobubble technology	Treatment of intravascular clot	IMA Rx Therapeutics
Phase 3	Combidex® / Ferumoxtran10	Iron oxide nanoparticle	MRI contrast agent	AMAG Pharmaceuticals
Marketed	Abraxane®	Albumin bound taxane particles	Non-small cell lung cancer	Abraxis Oncology
Marketed	AmBisome®	Liposomal preparation of amphotericin B	Fungal infection	Astellas Pharma US
Marketed	Doxil®	Liposomal doxorubicin	Ovarian tumour	Ortho Biotech

Nanoparticles come in a variety of forms, including inorganic, organic, nanocrystals, nanotubes, and polymeric structures like dendrimers. Their main applications are in medication delivery systems and research. The following is a list of the most prominent kinds of nanomaterials.

1. Nanotubes
2. Nanocrystals
3. Dendrimers
4. Liposomes
5. Solid lipid nanoparticles (SLNs)

Using a small, portable device that can accept small samples and process and analyze them nearly instantly, nanotechnology speeds up the procedure. The size of samples and biosensors used in in vitro diagnostic testing will only grow. Early detection of genetic abnormalities, tumors, and all disease states will be possible thanks to the formulations of nanoparticles for iron oxides and specialty polymers, which will boost their imaging capacity by employing lower and more effective concentrations of the diagnostic chemicals. Similar to biotechnology, nanomedicine has raised certain concerns in the past, most notably with regard to privacy and safety.[34]

Nanomedicine: A Revolution in Healthcare

The interdisciplinary field of nanomedicine is the result of the intersection of nanotechnology and medicine. A bioactive molecule can be guided to its desired location of action, its release can be controlled to ensure an optimal concentration at the therapeutic target over a desired time frame, and early disease detection and prevention can all

be made possible by nanomedicines, which are currently defined as nanoscale tools (e.g., 1–1000 nm sized) for the diagnosis, prevention, and treatment of diseases. The health care industry can benefit from a wide range of nanotechnology-based applications, such as the creation of novel diagnostic and imaging tools, stronger medications, drug delivery systems, implants, and gadgets. Thus, the process of identifying, treating, and avoiding illnesses and traumatic injuries through the use of currently created nanoscale-structured materials and basic nanodevices is known as nanomedicine.The interplay of these materials with biological systems lies at the heart of nanoscale-structured materials and nanodevices. In the long run, maybe in 10–20 years, molecular machine systems and nanorobots, a subset of nanomachines, may be added to the medical cannon of nanomedicine, providing doctors with the most powerful instruments to combat human illness, aging, and disease. Up till now, numerous classes of medical nanorobots have been designed, including respirocytes, clottocytes, vasculoids, and microbivores. Numerous illnesses, including cancer, excessive cholesterol, autoimmune disease, fungal infections, macular degeneration, hepatitis, and many more, can be treated with nanotherapeutics, which have already received FDA approval and are available for clinical use. Vaccinations, fluorescent biological labels, MRI contrast agents, pathogen detection, protein identification, DNA structure probing, tissue engineering, drug and gene delivery agents, and the separation of biological molecules and cells are among the other medical uses for NPs. an overview of FDA-approved medications, equipment, and diagnostics that make use of nanomedicine, as well as uses of nanomedical research.[35] While oncology has been the focus of the most recent nanomedical research and drug approvals, other diseases can also be treated with nanotherapeutic agents. For the treatment of serious fungal infections, there are multiple FDA-approved liposomal amphotericin B nano formulations available: Abelcet (Sigma Tau), AmBisome (Astellas/Gilead), and Amphotec. The FDA authorized these medications in 1995, 1997, and 1996, in that order. It has been demonstrated that liposomal formulations of amphotericin B are both safer and more effective than conventional formulations. Emend is an antiemetic medication used in patients undergoing chemotherapy or surgery. It has 40, 80, or 125 mg of aprepitant in the form of drug particles called Nano Crystals (Elan). Nano Crystal particles are drug substance NPs with a diameter of less than 1,000 nm that are created by a patented wet-milling method. The FDA gave Emend approval in 2003. Emend has a lower food impact and better absorption than previous traditional aprepitant formulations. For the treatment of hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia, Tri Cor (fenofibrate, Abbott) is recommended. Reformulated in 2004, Tri Cor utilizes Nano Crystal technology as well, taking the place of the prior traditional fenofibrate formulation. Lower dosages of the previously approved conventional Tricor formulation are equally safe and effective as higher dosages of the nano formulated version. Tri Cor's nano formulation also removed the need for the pills to be taken with food.

NANOSCALE DIAGNOSIS IN PARKINSON'S

Overview of Current Diagnostic Methods

A correct diagnosis is essential to the effective management of Parkinson's disease (PD). The various clinical symptoms of parkinsonism, such as bradykinesia, tremor, postural imbalance, dementia, sleep difficulties, sialorrhea, dry eyes syndromes and olfactory disturbances, exhaustion, and weight changes, are currently used to diagnose Parkinson's disease (PD). A key biomarker for Parkinson's disease (PD) diagnosis is the presence of Lewy bodies in the substantia nigra,

hypothalamus, basal nuclei, cranial motor nerve and its nuclei, etc. Various genetic and imaging tests were used to diagnose Parkinson's disease. Genetic mutation identification showed that autosomal-recessive inheritance is caused by D/1, Parkin, and PINK1, while autosomal-dominant inheritance is caused by a-synuclein, NURR1, LRRK2, and UCH-L1. Various diagnostic techniques, such as SPECT (single photon-emission computed tomography), MRI, transcranial ultrasound imaging, and PET (fluorine-18 labeled DOPA) imaging, are useful in differentiating and diagnosing Parkinson's disease (PD) from other neurodegenerative illnesses. For example, FP-CIT (N-w-fluoropropyl-2ß-carbomethoxy-3ß-(4-iodophenyl)nor tropane, a SPECT tracer utilized for presynaptic dopamine transporter imaging, binds to the DAT protein. As a result, the nigrostriatal dopaminergic transporter's integrity can be utilized as a diagnostic marker to identify early Parkinson's disease progression. Unfortunately, the expense and accessibility of these methods limit their applicability and efficacy in Parkinson's disease diagnosis. Figure provides a quick synopsis of the technologies created for Parkinson's disease diagnosis. Thus, innovative biomarker discovery, bioimaging modalities, and in vitro diagnostics are all incorporating nanotechnology to diagnose Parkinson's disease. There is still a need for well-established and validated biomarkers for Parkinson's disease. Because of this, the majority of current endpoints for evaluating patient response in clinics and large-scale clinical studies rely on patient response measures that are subjective and scores that are derived from scales such as the Unified Parkinson's Disease Rating Scale. These scales, which improved upon the traditional clinical features and assessed motor function in addition to response to levodopa medication, were designed to increase the precision of a clinical diagnosis. These scales still required a skilled clinician, though. Particularly in Parkinson's disease (PD), compensatory mechanisms can disguise the clinical characteristics for many years, and it is during this prodromal period that the disease continues to progress. Therefore, in order to define the criteria for the diagnosis of Parkinson's disease, a framework that incorporates clinical information, pathology, genetics, and molecular pathways along with objective testing needs to be devised. This has prompted initiatives such as the Parkinson's Progression Markers Initiative (PPMI), which is supported by the Michael J. Fox Foundation in an attempt to address the unfulfilled demand for appropriate biomarkers.

When diagnosing Parkinson's disease, a number of platforms are being examined to identify and measure these biomarkers, PD-associated diseases, imaging modalities, and clinical abnormalities. This article describes a range of nanoparticles that may be utilized to diagnose Parkinson's disease (PD). These nanoparticles can be made from zinc oxide, carbon nanotubes, fullerenes, etc.[36]

Detection of biomarkers

Clinical testing on blood, urine, and CS samples are being conducted as part of the PPMI project. Neuroimaging is being used to find improved markers of the early and accurate diagnosis of Parkinson's disease (PD) and its progression. Dopamine has long been measured by the use of chromatography and chromatography, methods that have been widely applied.

Mitochondrial dysfunction:

Another example is that Parkinson's disease (PD) has been linked to mitochondrial malfunction and the death of dopaminergic neurons has been linked to the suppression of complex I, which includes NADH: ubiquinone oxidoreductase. Ma and colleagues synthesized ubiquinone-quantum dot (CdSe/2nS) bioconjugates, wherein complex I and NADH could regulate the nanocomplex emission

by mimicking the electron-transfer system portion of the respiratory chain in mitochondria. The scientists demonstrated how the bioconjugates may be utilized to track complex I levels in human neuroblastoma SH-SYSY cells by tracking variations in fluorescence. This method, while still in the proof-of-concept phase, holds promise as an in vitro biosensor for PD early detection and disease progression tracking. Detection of a-synuclein: As previously mentioned, a-synuclein is a crucial neuronal protein linked to Parkinson's disease (PD). Current methods for quantitatively detecting it involve complex, time-consuming tools like size-exclusion chromatography, fluorescence measurements, NMR spectroscopy, and western blotting. Using gold-doped TiO nanotubes, An et al. created highly ordered microfabricated arrays for the photoelectrochemical detection of a-Synuclein. Primary antibodies were successfully immobilized on the arrays without compromising their stability or capacity to bind to a-synuclein. Subsequently by attaching the secondary antibody and glucose oxidase coated with gold nanoparticles, signal amplification was able to achieve outstanding sensitivity. Hydrogen peroxide and gluconic acid were produced from glucose by the action of glucose oxidase. The holes that generated within the valence band of the nanotubes may be scavenged by the peroxide upon irradiating the other side of the titanium foil. This resulted in a photocurrent proportional to concentrations of a-Synuclein, with an identifiable concentration in the range of pg/ml. Additional innovative ideas: A few more cutting-edge diagnostic ideas are beginning to take shape. One such development is the diagnosis of neurodegenerative conditions using breath testing. PD patients' breath has been discovered to include a variety of volatile chemical compounds, including hexadecane, butylated hydroxytoluene, and styrene. Tisch et al. used organically functionalized nanoparticles, such as carbon nanotubes and gold nanoparticles, as an example of how nanotechnology can be applied in the sensing of such new substances. With an accuracy of 78%, the sensors were able to differentiate the breath prints of Parkinson's disease from those of healthy states. In a similar vein, the technology may be able to distinguish Alzheimer's from Parkinson's illness.

Improved imaging technologies

Numerous complex imaging methods, including cranial CT, MRI, PET, and SPECT, are necessary for Parkinson's disease (PD). These methods are costly and typically only available in advanced healthcare facilities. There are a number of innovative methods under development that may be used to image Parkinson's disease and diagnose it earlier.

Challenges and Limitations

Present restrictions and difficulties with micro and nanotechnologies for PD treatment: production scaling and clinical application. Treatments with micro and nanotechnologies have showed a lot of potential. These systems can be prepared using various processes and developed with a broad range of materials. Simultaneously, advancements in micro and nanotechnologies are transforming the efficacy and safety of Parkinson's disease treatment. Although significant progress has been made, there are still important difficulties to overcome, as the majority of the studies covered in this review are still in the early phases of investigation. Figure 3 illustrates the main drawbacks and difficulties with using micro- and nanomedicines to treat Parkinson's disease (PD). These include the need for further research and development in the areas of clinical translation, safety concerns, manufacturing problems, and validated methods for characterizing micro- and nanomaterials. Better animal models are also needed. Approved techniques for characterizing nano- and micro medicines: Regarding particle size, shape, surface charge, polydispersity index,

and other factors, there is a great deal of variation in the research that have been published recently. The behavior and ultimate fate of MPs and NPs within the human body will be influenced by their distinct properties. Hence, it is necessary to construct validated procedures that assess the formulations' suitability in terms of their size distribution, shape, surface activity, surface charge, drug loading and release, crystal structure, aggregation, and physio-chemical characteristics, among other aspects. It is important to standardize the most appropriate material and biological characterization characteristics for each route of administration.

Improved animal models

As of now, the most widely used PD models entail the administration of neurotoxins such rotenone, 6-OHDA, and MPTP Journal of Controlled Release 295 (2019) 201-213. The symptoms and pathological features that are present in humans cannot be accurately replicated by these models. Therefore, it is imperative to create new animal models that accurately mimic every aspect of the disease, including pathological abnormalities such the creation of Lewy bodies and a-synuclein aggregation. In order to learn more about polo like kinase 2 (PLK2), a kinase that phosphorylates alpha-synuclein at Serine-129 (Ser-129) in Parkinson's disease, our lab has created a nanotechnology-based method [120]. The created nano system raises PLK2 intracellular levels in an attempt to mimic the gradually occurring neuronal alterations associated with Parkinson's disease (PD). It may also aid in our comprehension of the molecular pathways underlying a-syn phosphorylation and the assessment of potential treatment compounds.

Manufacturing issues:

There hasn't been any consensus up to this point regarding the best practices for designing MPs and NPs. Since this is the only way to transition production to an industrial lever, it is crucial to design a methodology based on the relevant manufacturing standard (GMP) and streamline the production processes. Furthermore, to pique industry interest, scalable approaches that are usable on a broad scale and have a good cost-effective connection must be implemented. In order to be able to engage in mutual consultation that permits advancement in the creation of such technologies, research and industry must establish a culture of partnership.

Clinical translation

The use of micro and nanomedicines in the treatment of many diseases has grown in strength. The largest number of medications in preclinical development and a sizable number of drugs that have been given FDA approval for clinical use are found in the cancer field. For other diseases like Parkinson's disease, however, the clinical use of this technique has not yet been accomplished. This shortcoming in the field of Parkinson's disease is made worse by the lack of clinical studies. There hasn't been a single registered clinical trial using micro or NPs to treat this illness as of yet. Actually, a significant portion of the research conducted up to now has only demonstrated effectiveness in rodent models of the illness .Therefore, more research is needed to confirm these findings in more relevant animal models or in more clinically relevant models, such the PD model in non-human primates. There are still more factors that prevent the application of micro- and nanotechnologies to clinical practice and the growth of their respective sectors, even in light of all the research covered in this review. It is crucial to stress once more that the primary obstacle to the advancement and development of successful treatments is still accurately describing and compressing the entire neuropathology of Parkinson's disease. These days, researchers are developing novel treatments that focus on distinct pathways or reasons. Nonetheless, it is necessary to design novel treatments that take the disease's

neurology into account.[37] For Parkinson's disease (PD), standard medication has a low therapeutic efficacy and merely provides symptomatic relief; in other words, it does not address the illness's progression or underlying cause and frequently results in treatment failure with a range of adverse consequences. For the proper treatment of Parkinson's disease (PD), the shortcomings of the available therapeutic modalities must be addressed.

Nanoscale Imaging Technologies

Quantum dots:

Although quantum dots (QDs) have special optical qualities, they are typically poisonous because of their composition, which frequently contains metals like zinc and cadmium. Coated QDs or modified core-shell QDs could be used to get around this. Single- or multi-walled carbon nanotubes can easily penetrate cells. But in the absence of any external or internal functionalization, they are immunogenic, cytotoxic, insoluble, and hydrophobic. Over time, the application of polymeric delivery methods has changed, with cationic polymers becoming more popular because of their capacity to bind anionic compounds like nucleic acids. The polymers that are selected also need to be stable in vivo, biocompatible, and biodegradable. Therefore, because of their abundance of cationic groups, polymers like dendrimers have become popular. These have also been used effectively as metallic NP stabilizers, such as AuNPs. The FDA-approved polymer poly (lactic-co-glycolic acid) has demonstrated promising qualities for use in drug delivery when combined with Au, and its PEGylated variants have been studied in AD. Liposomes, which are lipid-based NPs, have been widely employed to deliver bioactive substances, and some encouraging outcomes have been seen in animal models of AD.

Early Detection Advancements with Nanotechnology

Bioengineered nanoparticles that target and destroy cells, biocompatible tissue implantation, and nanosized implanted biosensors are just a few examples of the fascinating applications of nanomedicine for disease prevention, detection, therapy, and monitoring. The distinct qualities of nanoparticles may be leveraged at the molecular level, despite the fact that more ambitious applications, including multi-part nanomedical devices, have already been employed in mainstream medicine for fundamental nanomedicine applications like customized medications and medical equipment. On this small size, there is more surface area available for chemical attachment, making it easier to handle molecules and modify the behavior of particles. Additionally, nanomaterials are small enough to penetrate living cells.

Detection of cell loss:

A method based on immunostaining calbindin Dzsk, a protein found in afferent striatonigral fibers, was reported by Damier et al. in 1999 [71]. By applying this method to post-mortem specimens, scientists were able to identify 60% of all dopamine-containing neurons in the substantia nigra pars compacta within the high calbindin (nigral matrix) zone. The remaining 40% of neurons were discovered to be concentrated together as the zones with low calbindin (nigrosomes), appearing as invaginated pockets within the nigral matrix [71]. In comparison to controls, the study found that the mean loss in PD was greater than half of all dopamine-containing neurons. Furthermore, the substantia nigra pars compacta demonstrated a correlation between the length of the disease and the extent of dopamine-containing neuron loss. Thus, this experimental technique was used to find the pattern of cell loss in Parkinson's disease. This imaging method to monitor Parkinson's disease progression can be advanced through further developments in the imaging of cells employing quantum dots and gold

nanoparticles. Early disease identification became possible because to the use of carbon nanotubes, gold nanorods, and fast, low-cost detection techniques found in applications of nanotechnology for diagnosis. This method enhances patients' entire quality of life by using submicrometric equipment for better disease diagnosis, prevention, and treatment. Nanotechnology has the potential to significantly expedite the discovery of regenerative therapies. Patients with severe injuries or organ insufficiency can now receive prosthetic skin, bone, cartilage, or other tissues thanks to new techniques. Nanotechnology mimics the effects of natural tissues and organs by more efficiently altering cellular function.[39]

In advanced medical research across the globe, nanotechnology has been applied to both the diagnosis and treatment of Parkinson's disease. To diagnose Parkinson's disease (PD), a number of nano biosensors have been created thus far. These biosensors measure many biomarkers associated with PD, including dopamine, alpha-synuclein protein, homo vanilic acid, and even genetic mutations connected to PD. The benefits of employing nanoparticles and nanostructures in biosensors, particularly electrochemical nano biosensors, are embodied in nano bio sensors. Numerous studies have documented the benefits of using nanotechnology to increase the sensitivity of electrochemical nano bio sensors. Scientists have employed a variety of nanoparticles and nanostructures for the electrochemical nano bio sensor of Parkinson's disease detection, including gold nanoparticles, graphene, graphene oxide nanoribbons, single-walled carbon nanotubes, multi-walled carbon nanotubes, and electrochemically reduced fullerene-graphene oxide.

Nano biosensor Fabrication and Characterization:

The SPE's working surface was extensively cleaned with 50% ethanol before being followed by double-distilled sterilized water to create the Nano biosensor. After cleaning the SPE, a drop of EGO solution (final concentration of 8.0 mgL 1) was applied, and the area was let to dry. After that, the EGO-modified SPE was covered with a drop of GNWs (final concentration: 25.0 mg/mL 1), and the electrode was left in a sealed, humid container to gently dry. Field emission scanning electron microscopy imaging of the SPE surface was used to verify and check these production stages. After the working electrode was modified using the EGO and GNWs, 3.0 ml of a 220.0 nM solution was added to the electrode and it was stored in a humid container for 90 minutes to adhere to the GNW surface. Following a gentle wash with double-distilled water, the modified electrode was submerged in the MCH solution and then given another wash. The necessary concentration was quantified using the produced nano biosensor. In order to achieve this, a 3.0 ml drop of the necessary concentration of target miRNA was applied to the modified electrode's surface, allowed to sit for 90 minutes, and then cleaned with the washing solution. For eleven minutes, the hybridized nano biosensor was submerged in a 0.095 mM Dox solution to enable the Dox molecule to intercalate into the double-strand structure. After gently washing the modified electrode with double-distilled water, the DPV (with an amplitude of 25 mV, a modulation time of 0.05 s, and a step voltage of 50 mV) was carried out in a 0.1 MPBS solution with a pH of 7.0. Following each electrode modification step, the CV tests were conducted in 1.0 mMK3[Fe (C N)6] in PBS solution, with a sweep rate of 0.02 Vs 1 and a potential range of 0.025–0.33 V. To observe the changed electrode, the resulting CV curves were compared. Additionally, the target miRNA and several oligonucleotide solutions were tested in order to evaluate the produced nano bio sensor. In order to

test this, a particular concentration of target miRNA was made, hybridized with the nano biosensor, and the DPV curve was recorded. Subsequently, an oligonucleotide solution with a single nucleotide mismatch with the target miRNA was synthesized and examined in an identical manner to the target miRNA. The identical tests were conducted again using noncomplementary oligonucleotides, biosensors without any hybridization, and three-base mismatched oligonucleotides. In order to evaluate the developed system's selectivity, all of the DPVs were finally compared. Moreover, the created electrochemical nano biosensor was the subject of an actual sample research. A simulated sample of a Parkinson's disease patient was utilized to create a target miRNA solution using an isolated human serum as the medium. The created nano biosensor was used to assess three concentrations of miR-195 (30, 100, and 400 fMofmiR-195) spiked in the human serum collected for four replications. Calculations were made to determine the recovery percentage and relative standard deviation (RSD) % for each of the four replications.

NANOTHERAPEUTICS FOR PARKINSON'S

Traditional Parkinson's treatment

Parkinson expressed humility and possibly held an insight into modern neuroprotective theories when he expressed his wish for a cure that would allow "the progression of the disease to be stopped." In order to achieve this, he promoted extremely early therapeutic intervention when the symptoms were mostly limited to the arms and there were no problems with balance or walking. Parkinson suggested venesection, which mirrored early nineteenth-century therapeutic philosophies. He advocated bloodletting from the neck and the use of vesicatories to cause skin irritation and blistering. The objective of the small cork bits was to deliberately induce a "sufficient quantity" of purulent discharge within the blisters. With the goal of decompressing the medulla—which Parkinson believed to be the source of neurological dysfunction—all these measures were intended to shift blood flow and inflammatory pressure away from the brain and spinal cord. treatment using vibration. Charcot noted that after going for a carriage trip or going horseback riding, patients with Parkinson's disease had less rest tremor. He created a vibrating chair that was therapeutic and replicated the steady shaking of a carriage (Goetz 1996). Later, a vibrating helmet to shake the brain and head was created. [39]

Levodopa and Dopamine-Based Therapies

According to Hornykiewicz, G. Barger and J. Ewens synthesized dopamine for the first time in 1910. H. Dale found its modest sympathomimetic properties in the same year. These findings were subsequently brought to light by P. Holtz, who identified the enzyme dopa decarboxylase and proved that it converted levodopa into dopamine. At this point, dopamine was reduced to a simple molecule that served as an intermediary in the production of adrenaline and noradrenaline. But the constant finding of significant levels of dopamine throughout different organs spurred the hunt for a more central function. Hornykiewicz, who worked in Blaschko's laboratory at Cambridge University, examined how experimental animals' blood pressure was regulated and unequivocally established that dopamine acted independently of other catecholamines. Two important discoveries were made soon after, in the late 1950s: first, the location of dopamine in the brain, notably in the striatum; second, the creation of the reserpine model, which was eventually utilized as the first model of Parkinsonism that could be reversed with levodopa medication. When taken together, these findings quickly advanced theories of the part that dopamine loss plays in the etiology of Parkinson's disease, leading Bertler and Rosengred to

conclude that "dopamine is concerned with the function of the striatum and thus with the control of movement." After looking at a number of control specimens, Ehringer and Hornykiewicz switched their attention to the human brain and found that the brains of people with postencephalitic parkinsonism and Parkinson's disease had depleted striatal dopamine. Now that Hornykiewicz knew that levodopa was the natural precursor to dopamine, he was ready to recommend clinical trials with patients suffering from Parkinson's disease. After taking L-dopa [levodopa], patients who were bedridden and unable to sit up, stand up while seated, and begin walking were able to accomplish all of these tasks with ease. They were able to run and jump as well as move about with their usual associated gait. Pallilalia and slurred articulation obscured the voiceless, aphonic speech, which suddenly became clear and strong like that of a typical individual. A double-blind placebo-controlled trial was conducted after open-label levodopa trials using oral formulations revealed both short- and long-term benefits. Levodopa was established as the gold standard for treating the symptoms and signs of Parkinson's disease as a result of these observations. None of these developments compare to the first discoveries, despite the fact that novel formulations and peripherally acting dopa-decarboxylase inhibitors have given the therapy additional aspects.[39]

Nanoparticles in drug delivery

Targeted drug delivery

Adsorbed polymer matrices and nanoparticles containing one or more therapeutic medicines that can bind or scatter are the first components of nanotechnology-based drug delivery systems. Using imaging, therapies, and diagnostics, the manufacture of nanodrugs has advanced significantly in the past few years. The main goals of nano-drug systems are to lengthen the half-life of injectable medications, enhance the bioavailability of targeted tissue delivery, and administer medications orally. Nanoparticle medications provide pharmacological effects that are noticeably improved at lower dosages, with less risk to health and side effects. Considering they can shield the medication from chemical and/or biological deterioration and extracellular transport via P-glycoprotein efflux, nanoparticles (NPs) may provide an improvement in nose-to-brain drug administration. This would boost the availability of medications for the central nervous system (CNS).[40]

Controlled Drug Delivery on Parkinson's Disease

Dopamine Administration as A Physiological Approach

Improvements in adjuvant delivery techniques that lessen the negative effects of L-DOPA and its controlled release raise the prospect of creating PD therapies that are more potent. Reversing DA depletion research, however, might adopt a simpler strategy, concentrating on healthy physiological processes rather than diseased ones, in line with models in other domains. In this sense, current studies have concentrated on the release of dopamine (DA), which is ultimately the molecule required for dopaminergic activation, rather than precursors. Nevertheless, in contrast to L-DOPA, DA poses a number of issues with regard to its release and stabilization in vivo. DA is a highly reactive chemical in the first case. As a result of the dissociation of protons in their hydroxyl groups, free cytosolic DA can oxidize into dopamine-o-quinone and amino chrome, which produces superoxide radicals ($O2^{-}$). The neurodegenerative processes of Parkinson's disease (PD) are largely caused by oxidative products, which cause mitochondrial dysfunction through various means such as depolarization of the mitochondrial membrane, decreased ATP synthesis, accumulation of α-syn into neurotoxic protofibrils, dysfunction of the proteasome and

lysosome, and oxidative stress. Delivery mechanisms that enable the maintenance of the molecule's baseline state are thus necessary for the administration of DA, particularly at physiological pH levels. Furthermore, since monoaminergic synaptic vesicles have a pH that is 2 to 2.4 lower than the cytoplasm, the release should cause DA to be absorbed via them and prevent it from oxidizing. Not only must dopamine be preserved in its basic condition, but it also needs to be delivered under strict control so that dopaminergic neurons can utilize it as needed without experiencing overdosing. In this regard, Zhang et al. state that the release system must sustain physiological extracellular concentrations of dopamine (DA) (~23.2 μM in the cortex and ~332.6 μM in the striatum) and facilitate its primary utilization in the SNpc, the area previously identified as being primarily affected in Parkinson's disease (PD) and the starting point of the nigrostriatal pathway, which is responsible for fine motor control. To summarize, in order for DA delivery systems to be a practical alternative, they need to be able to stabilize DA in its basal form, promote a release under physiological conditions, and ensure that this release occurs in the appropriate regions—most notably the SNpc. Furthermore, as previously stated for the "overdosing theory" when DA is resituated in SNpc and VTA, the administration of these systems must not cause cytotoxicity or dosage-related side effects; therefore, biocompatibility and dosage must also be crucial considerations when developing these structures (a summary of these requirements is provided in Figure 3). Novel nanostructured devices for regulated release of docosahexaenoic acid (DA) have been created recently; these may serve as substitutes for the existing treatments for Parkinson's disease (PD) symptoms.

Nanocarriers for Controlled Release of Dopamine

One area of research in nanomedicine that is particularly interesting is the creation of nanostructured systems that have the ability to stabilize medications and release them under regulated conditions while maintaining dose and tissue selectivity. These kinds of nanostructures are known as nanocarriers, and they have huge surface areas and sub-micron diameters that stabilize increased loading or dosing per unit volume and increase a drug's bioavailability at the appropriate time and place. Because of the nature of their surface, their biocompatibility and selectivity can be increased by modifying the surface chemistry. Additionally, there is a lot of versatility in the ways that these nanocarriers can be administered.

Polymers and Derivatives:

In this regard, chitosan (CS) emerged as a key polymeric material for the creation and synthesis of polymeric NPs due to its biodegradability, biocompatibility, bioactivity, nontoxicity, and polycationic nature. Based on CS, there are numerous formulations for controlled drug release, including multiple DA release formulations. Trapani et al., for example, created CS-based nanocarriers with DA adsorbed on their surface. Acute intraperitoneal delivery of the polymeric NPs generated a dose-dependent increase in striatal dopamine output, according to in vivo investigations; in vitro study of the nanostructures revealed reduced cytotoxicity and a significant transport-enhancing effect in comparison to the control. In more recent methods, polymeric conjugates of esters and amides have been developed in an effort to functionalize the CS structure.Thanks to advancements, DA may now be delivered from the nose to the brain while avoiding spontaneous autooxidation thanks to nanocarriers that carry it over the blood-brain barrier. Nevertheless, it has been noted that once released, DA produces enhanced H2O2 production, despite the fact that CS NPs provide

neuroprotection by blocking DA oxidation and ROS generation. It's interesting to note that this is substantially less than the addition of pure DA. Accordingly, Ragusa et al. reported increased glutathione peroxidase and superoxide dismutase enzyme activity, which may be connected to CS NPs' ability to shield cells from DA-induced oxidative stress.[41]

Liposomes and Solid-Lipid NPs

A well-known class of drug carriers, liposome-like nanostructures have drawn a lot of interest because of their special qualities, which include improved drug delivery efficacy and biocompatibility. Liposomes have a considerably higher level of biocompatibility than other nanostructures since they are made of phospholipids, which can be derived from nature or surfactants, in contrast to polymeric NPs. Liposomes have the ability to sustain the physiological conditions required for dopamine transport in its baseline state (as in the case of presynaptic vesicles) and can potentially transport dopamine across the blood-brain barrier when it comes to controlled release of dopamine. The encapsulation of DA in liposomes and its controlled release effect in vivo were first accomplished by et al. For 25 days following the liposomes' stereotaxic implantation, the scientists measured the amount of dopamine (DA) in the striatal extracellular fluid using micro dialysis and evaluated apomorphine-induced asymmetric rotation. Moreover, they proposed that the liposomes' membrane composition may be changed to allow for longer-term encapsulation and release. After achieving stability of DA hydrochloride in positively charged liposomes for intraperitoneal administration, Jain et al. demonstrated an improvement in the symptomatology of rats with Parkinson's disease (in relation to the administration of L-DOPA) and demonstrated the liposomes' capacity to transport DA across the blood-brain barrier. Zhigaltsev et al. found that using an ammonium sulphate gradient to increase the DA/lipid ratio in DA-loaded liposomes completely compensates for dopaminergic deficit in the rat brain, in line with the same intraperitoneal injection protocol. Research has concentrated on surface functionalization to enhance encapsulation, recognition, and release in particular brain regions after DA encapsulation and transport in liposomes was confirmed. For example, Trapani et al. coated liposomes with thiolate CS to improve DA stability, which considerably protected DA from autoxidation to a larger degree than earlier CS NPs. Khare and colleagues, on the other hand, created glutamate-conjugated liposomes for receptor-mediated transcytosis delivery of DA, which demonstrated superior in vivo administration outcomes compared to standard DA-liposome delivery. In a similar vein, Lopalco et al. used transferrin, a hydrophilic carrier that controls extracellular iron, to functionalize DA-loaded liposomes.[42]

NEUROPROTECTIVE NANOPARTICLES

Brain-Targeted Biomimetic Nanodecoys with Neuroprotective Effects for Precise Therapy of Parkinson's Disease

By utilizing a rabies virus polypeptide (RVG29) for the modification of red blood cell membranes (RBCm), researchers successfully created nanodecoys encapsulating curcumin nanocrystals (CurNCs). These nanodecoys demonstrated effective shielding of dopaminergic neurons, improved blood-brain barrier (BBB) crossing, prolonged blood circulation, and evasion of Reticuloendothelial system (RES) absorption upon systemic delivery. In Parkinson's disease-afflicted mice, the incorporation of CurNCs within the nanodecoys led to the restoration of dopamine levels, suppression of α-synuclein aggregation, and correction of mitochondrial dysfunction. In vitro studies focusing on the neuroprotective effect of RVG29RBCm/CurNCs revealed good biocompatibility of Cur formulations in HSY5Y

cells at concentrations ranging from 1 to 20 μM. To determine the optimal modeling concentration for subsequent assessments, the impact of various concentrations of 1-methyl-4-phenylpyridinium ion (MPP+) on the viability of SHSY5Y cells was investigated. The ultimate optimum concentration for inducing sufficient cytotoxicity (approximately 40% cell viability inhibition) without causing significant cell damage was identified as 2 mM. Upon pre-treating SH-SY5Y cells with various Cur formulations, including Cur-NCs, RBCm/Cur-NCs, and RVG29-RBCm/Cur-NCs, considerable increases in cell viability were observed when exposed to 2 mM MPP+. This finding underscores the potential neuroprotective effects of these formulations in mitigating the detrimental impact of MPP+ on cellular viability, paving the way for further testing and development. Notably, therapy with RVG29-RBCm/Cur-NCs could greatly increase the survival rate (91.60%, 94.08%, and 98.26%, respectively) at the same therapeutic concentration (1, 5, and 10 μM). The enhanced rates of cell survival following treatment with Cur nano preparations were further confirmed by the live/dead cell staining data. Next, using Annexin V-FITC/PI staining, the antiapoptotic impact of RVG29-RBCm/Cur-NCs was investigated. Early and late apoptosis rates were used to compute the apoptosis percentage.27 The percentage of apoptosis was as high as 30.18% with MPP+ therapy. Following treatment with RVG29-RBCm/Cur-NCs, 9.44% was the substantial reduction in the apoptosis rate. This reduction showed the improved neuroprotection provided by RVG29-RBCm/Cur-NCs, as it was greater than that seen with Cur (23.90%), Cur-NCs (13.24%), and RBCm/Cur-NCs (11.20%). The fundamental cause of neuronal death is excess cytotoxic ROS produced as a result of MPP+ build-up disrupting the mitochondria. [28] In comparison to the MPP+ group, the intracellular ROS levels were decreased in the Cur treatment groups, and RVG29-RBCm/Cur-NCs exhibited the greatest therapeutic effect. Lastly, JC-1 labelling was used to examine the depolarization of the mitochondrial membrane in SH-SY5Y cells.29 Strong red fluorescence was seen in normal SH-SY5Y cells, which is indicative of a high mitochondrial membrane potential. By contrast, cells treated with MPP+ exhibited a green fluorescence signal, which is indicative of an early stage of apoptosis due to a lower mitochondrial membrane potential. By preventing the mitochondrial membrane from depolarizing, pre-treatment with RVG29-RBCm/Cur-NCs could raise the JC-1 fluorescence ratio to 90.45%. This recovery was in line with the flow cytometric analysis's finding of an antiapoptotic impact. Additionally, the administration of MPP+ resulted in high aberrant expression of α-syn, which was successfully suppressed by RVG29-RBCm/Cur-NCs. These findings suggested that Cur's neuroprotective effects could be amplified by Cur nano preparations. Compared to the RBCm/Cur-NCs and Cur-NCs groups, the RVG29-RBCm/Cur-NCs group had superior cell survival. This might have something to do with RVG29 change. Targeting the nAChR receptors expressed on SH-SY5Y cells, the RVG29-RBCm/Cur-NCs entered the cells via the receptor-mediated pathway and went on to play a neuroprotective function.[43]

Mitigating parkinsons disease

The most difficult barrier to overcome in the development of medications for encephalopathies is the blood-brain barrier (BBB), a physiological barrier in the brain. This barrier stops 98% of tiny molecules and almost all big molecules from entering the brain, regulating the flow of chemicals between the brain and the rest of the body. But the BBB's barrier function also prevents anti-PD medications from entering the body, making them ineffective. Consequently, despite the fact that a number of medications, including as curcumin,

matrine, and other natural compounds made from traditional Chinese medicines, have demonstrated encouraging anti-PD potential in vitro, they have not demonstrated equivalent effects in vivo. Many efforts have gone into developing ways to get medications past the BBB. These range from non-invasive techniques to the utilization of specific invasive injection methods. As a result, our understanding of the BBB's physiological roles is developing. Despite making up only 2% of the body weight, the brain is one of the most important organs since it needs 20% of the body's total energy to function normally. This high energy demand can be satisfied because the blood-brain barrier (BBB) has a variety of surface receptors and transporters that help transfer drugs across the BBB. Furthermore, lipophilic compounds can diffuse their way into the brain parenchyma with ease. Consequently, these physiological traits might be used to create medications that can pass across the BBB. The dopamine prodrug levodopa, which is frequently used in clinical settings, has a high permeability of the blood-brain barrier. However, because it isn't targeted well, it has poor potency. Enhancing the brain-targeting effectiveness of anti-PD medications is thus a significant medical problem. Drug delivery is becoming much more accurate and efficient because to advances in medical nanotechnology. This has rekindled optimism for the use of "old" medications, like pnictogen-based and herbal remedies. Numerous BBB-compliant techniques have been devised based on the physiology of the brain, and it has been demonstrated that several nanomaterials enhance medication transport to the brain. Many researchers have employed lipophilic drug carriers to enhance medication delivery to the brain since lipophilic compounds can readily pass the blood-brain barrier. Simple lipophilic carriers, however, are still inefficient since they cannot distribute drugs in a tailored manner. Ligands that precisely recognize BBB surface receptors or transporters are modified as drug carriers to enable receptor- or transporter-mediated BBB crossing for targeted drug administration. Despite the fact that these techniques have enhanced targeted delivery, they are ineffective, allowing the medicine to enter the brain without building up at the lesion site. Thus, effective nanomedicines with dual-targeting effects are needed to treat Parkinson's disease. Many BBB crossing techniques have been developed recently, including drug delivery using ultrasound and photothermal methods, developing nanomaterials that can penetrate cell membranes, and circumventing the BBB through nasal injection. It is anticipated that combining several tactics would enhance drug delivery that targets the brain and offer PD patients secondary tailored therapy. These anti-PD medications also have better clinical efficacy and fewer side effects.[44].

CHALLENGES AND ETHICAL CONSIDERATIONS

Safety Concerns in Nanomedicine

As there are currently no established and standardized methodologies available for the preclinical evaluation of micro- and nanomedicines, approaches that are both capable of predicting long-term medium toxicities and detecting acute toxic effects are needed. For example, the National Cancer Institute has assay cascade methods that are available for use in the context of cancer nano therapies. The examination of sterility and endotoxins, physical-chemical characterisation tests (size, size attribution, surface chemistry, solution characteristics, chemical composition), an in vitro characterization, and an in vivo evaluation of their effects are all included in this battery of testing. The recommendations contain the precise procedures that must be followed for each section and for every element required for the full characterisation of the nanodrugs. The development of standardized procedures in the area of micro and

nanotechnologies for PD treatment may benefit from this example. In summary, stringent safety requirements must be met throughout the whole study process to ensure that the results may be applied in a clinical context (from assessing the toxicity of chosen nanomaterials to determining the toxicity of micro/nanomedicines in pertinent preclinical models). Rushton et al. proposed a novel method for predicting toxicity assessment that involves comparing the steepest slope of the dose-response curves in vivo and in vitro. The greatest reaction per unit NP surface area, which was suggested as a novel response-metric, is comparable to the steepest slope when the NP surface area is used as the dose-metric to build the dose–response relationship. Using this idea, Rushton et al. found that, as shown by a pilot research involving eight NPs with varying physio-chemical composition and reactivity, the outcomes of in vitro cell-free and cellular assays showed a good predictive potential for in vivo inflammatory reactions. The researchers used the response-metric idea to analyse the findings of the aforementioned Says et al. study, which had not produced a sufficient in vitro–in vivo correlation, in order to test their methodology further. A very substantial in vitro-in vivo association was observed when the effect data from both the in vitro and in vivo experiments were translated to responses per unit surface area. Additionally, the authors proposed using this response-metric to develop a hazard rating that is based on the NP's reactivity per unit surface area, which is obtained from the examination of the dose-response connections. Such a category of hazards might be determined by varying endpoints assessed in particular tests. Since NPs are thus classified according to their biological activity rather than by a physio-chemical category (e.g., metal, metal oxides, polymers), a danger defined in this way would have practical significance. In addition, compared to NP surface area alone, this measure of reactivity per unit NP surface area might be a more accurate proxy for a biologically accessible surface.

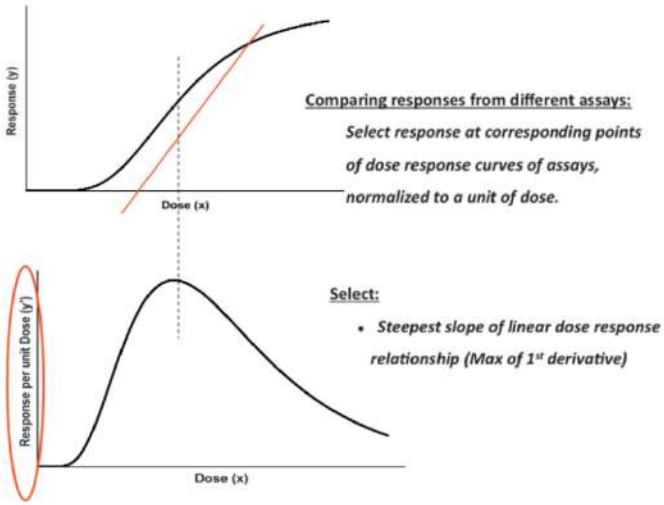

Fig. 1 Analysing complete dose–response relationships (from no-effect to supra-maximal effect doses, upper part of figure) of in vitro and in vivo assays of NPs to determine the steepest slope as an appropriate point for comparing responses across assays. This defines a response-metric in terms of the maximum response per unit dose (mathematically the first derivative, lower part of the figure). Using NP surface area as dose-metric for expressing the response-metric results in the best fit for correlating in vitro with in vivo responses. This concept needs to be validated with a broad range of NPs.[45]

Ethical implications of nanotechnology in healthcare The second most common neurodegenerative disease is Parkinson's disease (PD).In the substantia nigra pars compacta, dopaminergic (DA) neurons undergo selective death, resulting in the formation of -syn Lewy bodies. Familial Parkinson's disease has been linked to six mutations: SNCA, DJ-1, parkin, PINK1, ATP13A2, and LRKK2.Now that the relationship between -syn and PD development has been confirmed, researchers are looking for novel ways to disrupt its expression. A recent study loaded short hairpin RNA (shRNA) and an N-isopropylacrylamide derivative into magnetic iron oxide nanoparticles (NPs) by immobilizing them on oleic acid. N-isopropylacrylamide was additionally supplemented with nerve growth factor. Since ShRN effectively disrupted -syn production, it may be used to treat Parkinson's disease (PD). Moreover, retinoic acid NPs, a neuroprotective agent, have been employed and shown to be beneficial for DA neurons. Additionally, they stimulated the synthesis of mRNA and transcription factor proteins, Nurr 1 and PitX, which are essential for the survival of DA neurons. They can therefore be used to delay the onset of Parkinson's disease. Recently, curcumin and pipeline—which possess exceptional cognitive and antioxidant qualities—have been co-loaded onto glycerly monooleate nanoparticles. Multiple surfactants were coated on these NPs, increasing the loaded chemicals' bioavailability. Based on in vivo findings, they have the ability to suppress oxidative stress, apoptosis, rotenone toxicity, inhibit -syn, and limit the neuronal degeneration process of DA. Certain genes can be knocked down by RNA interference (RNAi). In one study, polyethylenimine NPs and -syn-targeting RNAi were utilized to treat Parkinson's disease (PD), an incurable neurological condition. [215]. The -syn level was lowered by about 50% in just 5 days, and no negative effects—such as toxicity induction—were noted. PEG has also been used to treat Parkinson's disease. Lactoferrin coating of PLGA-laden NPs improved the delivery of loaded rotigotine. The outcomes showed that its contact with the cells did not impair their viability. Free rotigotine was actually toxic. Additionally, a significant concentration of rotigotine was reported to be unevenly transported to the striatum, the principal region affected by Parkinson's disease (PD).[46]

Gene therapy

One potential application of nanomedicine is the controlled delivery of genes to the brain. Since viral vectors have toxicity and immunogenicity issues, a lot of research has gone toward developing non-viral vectors such polymeric NPs, which could lead to a safer and nontoxic gene delivery technique. The use of polymeric Ns for miR-124 administration is one particularly intriguing example in the development of nanomedicines for microRNA delivery. According to Saraiva et al., miR-124-loaded NPs were stereotactically injected into the right lateral ventricle of mice treated with 6-OHDA. This resulted in neurogenesis in the subventricular zone, which encouraged the migration and integration of mature neurons into the lesioned striatum and alleviated motor symptoms. In a similar manner, human GDNF-encoding DNA has also been nanoencapsulated. These Ns are generated from a plasmid DNA molecule that has CK30PEG10k, a 30-mer lysine polymer that has been replaced with polyethylene glycol, appended to it. This combination can transfect postmitotic cells and transfer plasmids to brain cells. Animals given GDNF-encoding DNA NPs had better motor performance and more nigral dopaminergic neurons in their brains. Additionally, TH+ fibers in the injured striatum were partially protected. This work represents an initial demonstration that synthetic Ns could efficiently transfer therapeutic

genes to the brain and, upon transgenic expression, have a neuroprotective impact.[47]

Balancing risk and benefit

Boost the effectiveness of drugs A fascinating field of study that has the potential to help pharmaceutical firms reduce some systematic adverse effects and increase the effectiveness of current medications is drug delivery via smart materials and nanoparticles. It is composed of assemblies of transport agents; drugs and imaging equipment are designed to target the impacted tissues and track the process at the same time. Stated differently, the distinct functional requirements must be differentiated into the essential physical-chemical attributes and linked to biological behaviour. Handling of sickness An increasingly useful technique for treating and preventing disease in the face of global bacterial resistance to antibiotics is nanotechnology. When combined with antibacterial substances like nano-silver, the effectiveness of bacterial membranes at the nanoscale can be even more remarkable. When incorporated into conventional materials, these characteristics can reduce the requirement for medicines while safeguarding the patient against infection. Treatment for patients could be revolutionized by nanotechnology. This technology is still a long way from becoming ubiquitous in life science research and development and other areas of the healthcare industry. Given the rising cost of healthcare and the high cost of life science research and development, the current economic climate in which nanotechnology is at the forefront of healthcare treatment may prove to be too challenging and dangerous to justify investments. Oral painkillers are typically administered more easily and with sufficient comfort for the patient.

Nanobots

Nanobots are the most important development in nano medicine. It is possible to use nanobots to replace entire intracellular components and repair damaged cells. Moreover, they can be duplicated to fix a genetic flaw or swap out a DNA molecule to eradicate an illness. Medical nanobots have the potential to revolutionize healthcare by performing procedures like artery unblocking or organ replacement. Despite its ability to deliver precise dose concentrations to targeted areas, nanocarriers' small size forces a paradoxical trade-off between manufacturing volume and quality. Artificial intelligence-driven coordinated behaviour and communication will enable nanobots to carry out their missions methodically and effectively. It is possible to independently program, search, and move nanobots in different directions. A single nanobot can establish connections with friends and colleagues, each following their own set of rules, and request that they group their coatings, loads, or sizes in order to more effectively monitor the presence, diagnosis, or targeting of diseased tissues.[48]

RECENT BREAKTHROUGHS AND CASE STUDIES

Noteworthy Research and Development

Nowadays, a number of studies are being conducted on nanotechnologies to explore their potential for use in drug delivery, therapeutics, and diagnostics. Drug delivery systems based on nanotechnology have been used recently to help successfully deliver medications to their intended locations. Receptors on cell membranes or proteins on cell surfaces are typically the primary targets in bodily systems. Currently, a variety of nanocarriers are developed with distinct drug release patterns and approaches to increase the chemical functionalization of the drug molecules' selectivity towards the target location. In the coming years, nanotechnology will be crucial to revolutionizing medicine. By 2028, cardiovascular disorders including atherosclerosis may be treated with nanorobotic instruments. With the use of this technology, cancer cells can be destroyed and infections can be reduced by stimulating the

immune system. Anticancer medications can be delivered specifically to treat malignant and precancerous cells by nano oncology. In the upcoming years, nanotechnology will aid in the health care system's evolutionary development.[49]

Global indicators of the development of nanotechnology, 2000–2020

The following table, which lists six important metrics, illustrates the return on investment for efforts made in the advancement of nanotechnology and related scientific and technical advances. Based on these statistics, global average yearly growth rates between 2000 and 2008 were almost 25%. Figures for the world are bolded, whereas figures for the US are italicized. Titleabstract keywords were used to search SCI publications and patent applications, using Chen and Roco's (2009) methodology. Lux Research provided the venture capital estimates; refer to Chapter 13, Sect. 13.8.11 a Roco and Bainbridge (2001). During the 2009 financial crisis, the average growth rates of all indicators decreased by more than half globally. 2010 seems to be seeing a return to greater rates than 2009, while there are notable variations throughout countries and relevant domains.[50]

Table six key indicators of nanotechnology development in the World and US

World /US/	**people primary workforce**	**SCI papers**	**Patent application**	**final product market**	**R&D funding public + private**	**Venture capital**
2000 (actual)	**~60,000** /25,000/	**18,085** /5342/	**1,197** C	**~$30 B** /$13 B/	**~$1.2 B** /$0.37 B	**~$0.21 B** /$0.17 B/
2008 (actual)	**~400,000** /150,000/	**65,000** /15,000/	**12,276** /3,729	**~$200 B** /$80 B/	**~$15 B** /$3.7 B/	**~$1.4 B** /$1.17 B/
2000-2008 (average growth)	**~25%**	**~23%**	**~35%**	**~25%**	**~35%**	**~30%**
2015 (2000 estimate)	**~2,000,000** /800,000/			**~1,000 B** /$40 B/		
2020 (extrapolation)	**~6,000,000** /2,000,000/			**~$3,0000 B** /$1,000 B/		

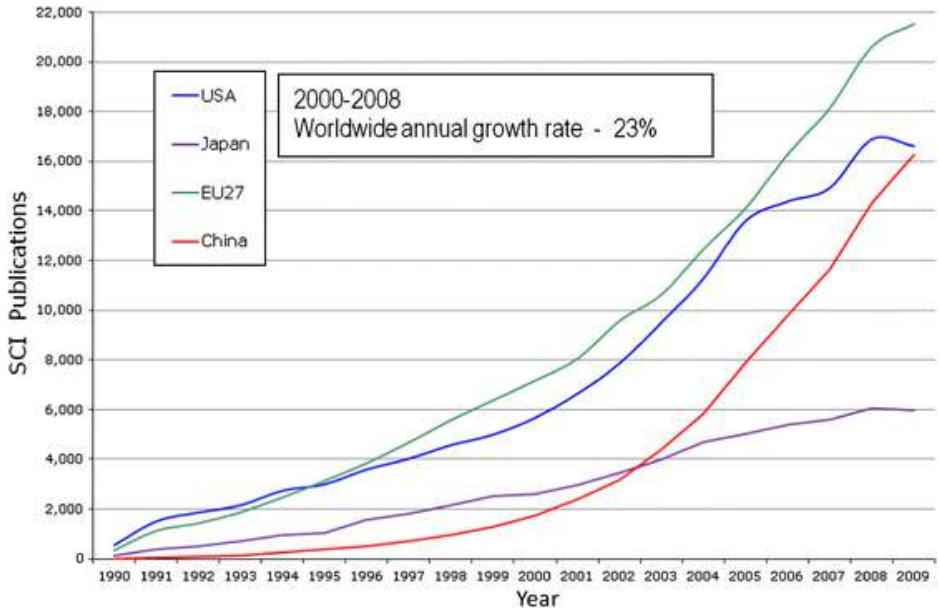

Fig. 2 Nanotechnology publications in the SCI 1990–2009. Data was generated from an online search in the Web of Science using a ‘‘title–abstract’’ search in SCI database for nanotechnology by keywords (courtesy of H. Chen, Y. Dang, and M. Roco)

Successful Implementation of Nano solutions

Parkinson's disease is a neurodegenerative condition that causes the brain's corpus striatum to lose dopamine as a result of the death of nigrostriatal dopaminergic neurons. Postural irregularities, bradykinesia, tremor, and muscle rigidity are among the main signs of Parkinson's disease. Therefore, the most prevalent usage of dopamine precursor L-dopa is in the treatment of Parkinson's disease. Polymeric nanoparticles are a type of nanotechnological medication delivery technology for neurodegenerative diseases like Parkinson's disease (PD). These particles can target mutagenesis proteins and traverse the blood-brain barrier to achieve high drug loading capacity. Implantable biosensors with nanowires are also being developed to treat Parkinson's disease. There are new treatments in the works that use drug delivery methods to treat Parkinson's disease. The benefits that micro- and nanoparticles (MPs and NPs) provide over traditional therapy are drawing a lot of attention to them. These systems offer sustained release over time, which lowers the frequency of drug administration and lowers the risk of dose dumping associated with other controlled release systems developed in the past, such as hydromorphone hydrochloride prolonged-release capsules (marketed as Palladone™). Moreover, NPs facilitate drug passage across the blood-brain barrier (passive targeting). Furthermore, the immobilization of BBB cell-specific ligands, such as transferrin receptor antibodies, might functionalize the NPs' surface and improve their overall systemic effects by facilitating NP transit to the brain parenchyma (active targeting). [51] The viability and potential of this approach have been demonstrated by the effective encapsulation of a number of hydrophobic or hydrophilic medicinal compounds for Parkinson's disease (PD) in particles while preserving their biological activity. Particles can be administered to the brain using three different methods for PD therapy: local, systemic, or intranasal. Since MPs' bigger size makes alternative administration methods difficult to use, local administration in this context mostly refers to the delivery of MPs by stereotactic surgery. On the other hand, less intrusive methods of delivering NPs, like systemic and intranasal administration, might work. Researchers have specifically

concentrated on the use of the intranasal route as a non-invasive approach that reduces systemic exposure by avoiding the blood-brain barrier and delivering medications straight to the brain. These systems still represent a relatively untapped area for PD therapy, although having already demonstrated their potential in other domains, like as cancer therapy. Accordingly, the majority of research on the delivery of molecules in MPs or NPs for this illness have mostly been conducted on smaller, clinically relevant animal models (such as mice and rats), with a small number also being conducted on larger, non-human primate models. [52]

Impact on patient outcomes

It appears plausible to expect related issues and hazards to human life in the future given the wide range of applications of nanomaterials in all facets of life today and their growing introduction into biosystems, such as soil, water, and air. Nanotechnology is a huge help in our understanding of the pathogenesis of Parkinson's disease. Nanoparticles can be used to image early neuronal death, and nanodevices can be used to identify and quantify amyloid peptides in cerebrospinal fluid. Nanomaterials have been investigated for the delivery of antiparkinsonian medications, neurotrophic factors, antioxidants, neuroprotective, and antiapoptotic chemicals in experimental models of Parkinson's disease. The loss of dopamine-releasing neurons causes a reduction in motor capacities, which is indicative of this condition [Sharma et al., 2021]. Among the several options for treating disease, nanoparticle-based technology is positioned as a leading method due to the vast array of nanomaterials that provide favourable qualities for theragnostic drug delivery strategies. The formulation of dopamine-loaded nanoparticles has been studied to change the stability, efficacy, and bioavailability of therapy. Different types of nanomaterials have been developed to enclose dopamine: liposomes, chitosan nanoparticles, quantum rods, cellulose acetate phthalate, co-modified nanoparticles of borneol and lactoferrin, and solid lipid nanoparticles. To the best of our knowledge, however, no research has been completed for the clinical therapy of Parkinson's disease. Preclinical Parkinson's disease models have already been used to test a few of these nanomaterial-based technologies [MongeFuentes et al., 2021].[53]

Future Prospects and Trends

Depending on their unique composition, nanozymes might have different reaction processes. Non-metallic nanozymes, like those based on carbon, have an aromatic ring that functions similarly to the porphyrin ring seen in natural enzymes by facilitating electron transfer (Gao et al., 2020). Natural metalloenzymes' metal catalytic active site is mimicked by metal sites found in metal oxide nanozymes. When hydrogen peroxide is present, metal oxide nanozymes have the propensity to act as peroxidases, which allows them to catalyse the oxidation of a chromogenic substrate (Gao et al., 2020). Because they can flip between oxidation states, some metal oxide nanoparticle systems, such cerium oxide, can imitate many enzymes at once and exhibit a mechanism similar to redox enzymes (Yang et al., 2016; Hegazy et al., 2017). By creating bimetallic nanoparticles, such as the PtCu system that is covered below, metal-based nanozymes can be enhanced. Bimetallic nanozymes have the ability to mimic one or more enzymes at once, and they can be used to modulate the catalytic activity of a system by varying the metal ratio (He et al., 2017; Liu et al., 2020). Nanomaterials have the ability to lessen oxidative stress, as shown by cellular PD models. Ruotolo et al. investigated how cerium oxide NPs (CeO2 NPs) affected a yeast cell culture that was overexpressing human α-syn. The findings demonstrated that CeO2 NPs counteracted α-syn-induced mitochondrial damage and dramatically reduced α-syn

cytotoxicity in a dose-dependent manner by inhibiting the development of α-syn cytoplasmic inclusions. After being exposed to CeO2 NPs, yeast cells expressing α-syn had reduced levels of mitochondrial fragmentation, a greater quantity of mitochondria that were actively working, and a notably reduced amount of free radicals (Ruotolo et al., 2020). Hao et al. (2019) used a neural cell model of Parkinson's disease (PD) produced by 1-methy-4-phenylpyridinium (MPP+) to show how copper-based NPs, in particular Cu2O and CuO, may reduce ROS. Hao carries out more research on mice by using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce Parkinson's disease. According to the study's findings, CuxO nanoclusters reduce neurotoxicity by imitating the actions of glutathione peroxidase, superoxide dismutase, peroxidase, and catalase (Hao et al., 2019). Singh et al. (2017) discovered that Mn3O4 nanozymes efficiently mimic SOD, catalase, and glutathione peroxidase—three important antioxidant enzymes with typically cytoprotective activities that are hindered in Parkinson's disease (PD)—in another cellular investigation employing an MPP+-induced PD model. Given that each major antioxidant enzyme has a distinct function in the fight against oxidative stress, the capacity of Mn3O4 nanozymes to imitate all three of these enzymes concurrently is noteworthy. Furthermore, in plant-based models, it has been discovered that simultaneous expression of all three key antioxidant enzymes improves tolerance to oxidative stress (Lee et al., 2007; Sharma et al., 2012). Liu et al. (2020) used α-syn preformed fibrils (PFF) injection to induce sporadic Parkinson's disease (PD) in animals and neuronal cells. The antioxidant capacity of PtCu bimetallic nanoalloys (NAs) was measured by employing the standard radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). PtCu NAs are potential antioxidants because, as Liu et al. (2021) showed, they exhibit peroxidase, catalase, and SOD-like activity in addition to their ability to scavenge DPPH. The findings of their investigation demonstrated that the PtCu nanozyme is highly effective in stopping the propagation of prion-like α-syn in Parkinson's disease (PD) (Liu et al., 2020; Figure 1E). Redox nanozymes have the potential to be effective therapeutic techniques in stopping the abnormal spread of α-syn, as evidenced by the study's proof of concept. It would be beneficial to conduct more research on optimizing nanozymes to prevent prion-like proliferation, as nanozyme therapy might be used as a successful method for treating prion-like proteinopathies like Parkinson's disease.

NANOTECHNOLOGY APPROACHES TARGETING FIBRILLIZATION PROCESSES

Nanomaterials Approaches Targeting α-Synuclein Aggregation in PD

Targeting the misfolded α-syn fibrils themselves or limiting their enhanced expression are two strategies to reduce α-syn aggregation. Here, we address modified exosomes that target the central nervous system to deliver α-syn siRNA and block α-syn translation, as well as graphene quantum dots and cerium oxide NPs, which bind to α-syn and disaggregate fibrils directly. Graphene quantum dots (GQDs) are nanoparticles (NPs) that are made up of graphene layers and have a diameter of about 100 nm. According to Kim et al. (2018), GQDs may effectively cross the blood-brain barrier and attach themselves to α-syn fibrils. This process prevents α-syn fibrillization and breaks down fibrillated α-syn in a time-dependent way. GQDs also prevented α-syn PFFs from being transmitted. GQDs have also been shown by Kim et al. to exhibit neuroprotective qualities. GQDs were reported to alleviate the effects of α-syn-induced mitochondrial damage, decrease the production of Lewy bodies and neurites, and restore lowered synaptic protein levels after treating α-syn PFFs-induced synaptic dysfunction and mitochondrial damage. Furthermore, neither

in vitro nor in vivo did GQDs result in any appreciable long-term toxicity (Kim et al., 2018). Even though studies have shown that GQDs have a protective impact, more research is necessary to fully comprehend the mechanisms. Furthermore, as was previously mentioned in section 2.1, recent molecular docking studies have demonstrated that cerium oxide NPs fit best into the α-syn active site and disaggregate fibrillar α-syn in vivo when compared to other biomaterials like gold and superparamagnetic ironoxide NPs (Kaushik et al., 2018; Zand et al., 2019). Ruotolo's study found that CeO2 NP administration dramatically reduced α-syn cytotoxicity in a dose-dependent manner by inhibiting the formation of α-syn cytoplasmic inclusions and decreasing mitochondrial damage in a yeast model with cells overexpressing human α-syn (Ruotolo et al., 2020). Another way to lower the levels of misfolded α-syn is to change the expression of the α-syn gene. Exosomes can be altered to improve delivery, as demonstrated by Cooper et al.'s use of the rabies virus glycoprotein peptide (RVG) specific to the central nervous system to transport siRNA and decrease α-syn expression. Alpha synucleinopathies can be delayed and reversed by delivering α-syn siRNA via the modified RVGexosome (Cooper et al., 2014).

Predictions for the future of parkinsons disease

Concerns about the toxicity of NPs are among the new and present research difficulties in NPs. Studies have demonstrated that the same characteristics that give NPs their advantages could also be responsible for their harmful consequences (Aillon et al., 2009; Song et al., 2016; Mohammadi and Nikkhah, 2017). Reactive oxygen species produced by NPs typically result in oxidative stress, which is the cause of neurotoxicity (Teleanu et al., 2018). Nonetheless, some alterations lead to improvements in NP biocompatibility. Going forward, it will be necessary to fully investigate and address NP toxicity and make attempts to minimize or completely eradicate any harmful effects during the growth stage. NPs' composition, size, shape, and charge all seem to have an impact on the pathogenic protein aggregation process. To understand how NPs behave in different combinations of these variables, more research is required. Finding the most effective NP-based treatment for neurodegenerative illnesses requires both in vitro and in vivo research. Furthermore, the latest developments in nanozymes offer promising new avenues for tackling inflammation and oxidative stress in AD and PD; however, additional research is necessary to ensure safe clinical application. Understanding the catalytic mechanisms of nanozymes will be essential for optimizing the composition, capabilities, and control of catalytic activity. To guarantee the security and effectiveness of nanozyme therapy, more research on the biocompatibility and nano bio interactions of nanozymes is necessary (Wang et al., 2018; Tian et al., 2020).A multitude of drug delivery strategies are made possible by the flexibility and modifiability of different nanomaterials, which improve transport across the blood-brain barrier, allow for targeted delivery or additional functions, accommodate different drug chemistries and solubilities, and evade immune system detection. Materials like hydrogel scaffolds may be essential in regenerative medicine, which attempts to repair the damage caused by neurodegeneration, in order to create the ideal physical and milieu for supporting neuronal development and axonal extension. But more research is needed to determine the best medication combinations and microenvironments. The field of treating neurodegenerative diseases with nanomaterials is constantly expanding, with the potential to both revolutionize the delivery of therapeutic drugs and develop a completely new class of medicines that address conditions that are traditionally difficult to treat.[54]

CONCLUSION

The integration of nanotechnology into the realm of Parkinson's disease research holds tremendous promise for advancing diagnostics and therapeutics. The reviewed literature demonstrates that nanomaterials can effectively address challenges associated with drug delivery, blood-brain barrier permeability, and limited bioavailability in traditional treatments for Parkinson's disease. Nanoparticles, including various formulations such as liposomes, polymeric micelles, and dendrimers, offer unparalleled opportunities for targeted drug delivery to the brain. Their ability to improve pharmacokinetics and enhance the therapeutic index of drugs opens new avenues for developing more effective treatments with reduced side effects. Furthermore, the application of nanotechnology in imaging techniques provides valuable tools for early diagnosis and monitoring disease progression. Nanoscale platforms not only enable precise visualization of pathological changes but also offer potential for personalized and precise interventions. While the field of nanotechnology in Parkinson's disease is still in its nascent stages, this review highlights the encouraging progress made thus far and emphasizes the need for continued research and development. Overcoming challenges such as biocompatibility, long-term safety, and scalability will be crucial for translating these promising findings into practical clinical applications. In the years to come, the synergy between nanotechnology and Parkinson's disease research is expected to usher in a new era of innovative and targeted therapies. As researchers continue to unravel the complexities of this neurodegenerative disorder, the integration of nanotechnology may pave the way for transformative advancements in patient care and management. This comprehensive overview aims to inspire further investigations, collaborations, and clinical trials, ultimately contributing to the development of effective and personalized strategies to combat Parkinson's disease.

REFERENCES

1. Jagaran K, Singh M. Nanomedicine for neurodegenerative disorders: Focus on Alzheimer’s and Parkinson’s diseases. International Journal of Molecular Sciences. 2021 Aug 23;22(16):9082.
2. Adhikary RR, Sandbhor P, Banerjee R. Nanotechnology platforms in Parkinson’s Disease. ADMET and DMPK. 2015 Sep 5;3(3):155-81.
3. T. Pringsheim, N. Jette, A. Frolkis, T.D.L. Steeves, Mov. Disord. 29 (2014) 1583-1590.
4. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harbor Perspectives in Medicine:. 2011 Sep;1
5. Idrees M. Role of nanotechnology in medical sciences: a review. Int. J. Drug Discovery. 2015;5:14-24.
6. Zajtchuk R. New technologies in medicine: Biotechnology and Nanotechnology. Disease-a-Month, 45 (11), 1999, 453 95.
7. Roszek, Boris WH, De Jong and Geertsma RE. Nanotechnology in medical applications: state-of-the-art in materials and devices, 2005.
8. Silva GA. Introduction to nanotechnology and its applications to medicine. Surgical neurology. 2004 Mar 1;61(3):216-20.
9. Hu, EL, Shaw, DT. Synthesis and assembly. In: Siegel RW, Hu EL, Roco, MC, eds. Nanoscience Structure and Technology. National Science and Technology Coun- cil, 1999.
10. Hanes J, Cleland JL, Langer R. New advances in microsphere-based single dose vaccines. Adv Drug Del Rev 1997;28:97–119.
11. LaVanDA,LynnDM,LangerR.Movingsmaller indrug discovery and delivery. Nat Rev Drug Discov 2002;1: 77–84

12. Rhaman MM, Islam MR, Akash S, Mim M, Nepovimova E, Valis M, Kuca K, Sharma R. Exploring the role of nanomedicines for the therapeutic approach of central nervous system dysfunction: At a glance. Frontiers in Cell and Developmental Biology. 2022 Sep 2;10:989471
13. Silva, G. A. J. B. (2008). Nanotechnology approaches to crossing the blood-brain barrier and drug delivery to the CNS. BMC Neurosci. 9, S4–S4. doi:10.1186/1471- 2202-9-S3-S4
14. Adhikary RR, Sandbhor P, Banerjee R. Nanotechnology platforms in Parkinson's Disease. ADMET and DMPK. 2015 Sep 5;3(3):155-81
15. Reichmann H. Clinical criteria for the diagnosis of Parkinson's disease. Neurodegenerative diseases. 2010 Jul 9;7(5):284-90.
16. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. Journal of neurochemistry. 2016 Oct;139:318-24.
17. Perez-Lloret S., Negre-Pages L., Ojero-Senard A. et al. for the COPARK Study Group. (2012). Oro-buccal symptoms (dysphagia, dysarthria, and sialorrhea) in patients with Parkinson's disease: preliminary analysis from the French COPARK cohort. Eur. J. Neurol. 19:28–37
18. Schrag A., Horsfall L., Walters K. et al. (2015) Prediagnositc 0presentations of Parkinsons disease in primary care: a case-control study. Lancet Neurol. 14, 57–64.
19. Jost W. H. (2003) Autonomic dysfunction in idiopathic Parkinson's disease. J. Neurol 250(Suppl 1), 28–30
20. Larsen J. P. and Tandberg E. (2001) Sleep disorders in patients with Parkinson's disease: epidemiology and management. CNS Drugs 15, 267–275.
21. Hughes AJ, Daniel SE, Kilford L, Lees AJ: Ac- curacy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
22. Hughes AJ, Daniel SE, Kilford L, Lees AJ: Ac- curacy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
23. Antonini A, Vontobel P, Psylla M, et al: Complementary positron emission tomographic studies of the striatal dopaminergic system in Parkinson's disease. Arch Neurol 1995;52: 1183–1190
24. Mendonca DA: Tasks of attention augment rigidity in mild Parkinson disease. Can J Neurol Sci 2008;35:501–505.
25. Marttila RJ, Rinne UK: Disability and progression of Parkinson's disease. Acta Neurol Scand 1977;56:159–169
26. T. B. Stoker and J. C. Greenland, Parkinson's Disease: Pathogenesis and Clinical Aspects [internet], 2018, DOI: 10.15586/codonpublications.parkinsonsdisease.2018
27. Kulkarni AD, Vanjari YH, Sancheti KH, Belgamwar VS, Surana SJ, Pardeshi CV. Nanotechnology-mediated nose to brain drug delivery for Parkinson's disease: a mini review. Journal of drug targeting. 2015 Oct 21;23(9):775-88
28. Bjorklund T, Kirik D. Scientific rationale for the development of gene therapy strategies for Parkinson's disease. Biochim Biophys Acta 2009;1792:703–13.
29. Wijeyekoon R, Barker RA. Cell replacement therapy for Parkinson's disease. Biochim Biophys Acta 2009; 1792:688–702.
30. [30] Alabrahim OA, Azzazy HM. Polymeric nanoparticles for dopamine and levodopa replacement in Parkinson's disease. Nanoscale advances. 2022;4(24):5233-44.

31. Roco, M.C. The long view of nanotechnology development: the National Nanotechnology Initiative at 10 years. J Nanopart Res 13, 427–445 (2011
32. Roco MC, Williams RS, Alivisatos P (eds) (1999) Nanotechnology research directions: Vision for the Next Decade. Springer (formerly Kluwer Academic Publishers) IWGN Workshop Report 1999. Washington, DC: National Science and Technology Council. Also published in 2000 by Springer.
33. Omanović-Mikličanin E, Maksimović M, Vujović V. The future of healthcare: nanomedicine and internet of nano things. Folia Medica Facultatis Medicinae Universitatis Saraeviensis. 2015 Jun 30;50(1):23-8.
34. Ventola CL. The nanomedicine revolution: part 2: current and future clinical applications. Pharmacy and Therapeutics. 2012 Oct;37(10):582.
35. G. Miller, M. Kearnes, Nanotechnology, Ubiquitous Computing and The Internet of Things: Challenges to Rights to Privacy and Data Protection, Draft Report to the Council of Europe, 2012
36. Adhikary RR, Sandbhor P, Banerjee R. Nanotechnology platforms in Parkinson's Disease. ADMET and DMPK. 2015 Sep 5;3(3):155-81.
37. Torres-Ortega PV, Saludas L, Hanafy AS, Garbayo E, Blanco-Prieto MJ. Micro-and nanotechnology approaches to improve Parkinson's disease therapy. Journal of Controlled Release. 2019 Feb 10;295:201-13.
38. Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of Nanotechnology in Medical field. Global Health Journal. 2023 Feb 25
39. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med. 2011 Sep;1(1):a008862. doi: 10.1101/cshperspect.a008862. PMID: 22229124; PMCID: PMC3234454
40. Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of Nanotechnology in Medical field. Global Health Journal. 2023 Feb 25
41. Ahmad J, Haider N, Khan MA, Md S, Alhakamy NA, Ghoneim MM, Alshehri S, Imam SS, Ahmad MZ, Mishra A. Novel therapeutic interventions for combating Parkinson's disease and prospects of Nose-to-Brain drug delivery. Biochemical Pharmacology. 2022 Jan 1;195:114849.
42. Padilla-Godínez FJ, Ruiz-Ortega LI, Guerra-Crespo M. Nanomedicine in the face of Parkinson's disease: from drug delivery systems to nanozymes. Cells. 2022 Oct 31;11(21):3445
43. Liao J, Fan L, Li Y, Xu QQ, Xiong LY, Zhang SS, Liu JH, Xiao ZC, Zhang C, Yang J, Chen ZS. Recent advances in biomimetic nanodelivery systems: New brain-targeting strategies. Journal of Controlled Release. 2023 Jun 1;358:439-64.
44. Cheng G, Liu Y, Ma R, Cheng G, Guan Y, Chen X, Wu Z, Chen T. Anti-Parkinsonian therapy: strategies for crossing the blood–brain barrier and nano-biological effects of nanomaterials. Nano-micro letters. 2022 Dec;14(1):105
45. Oberdörster G. Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. Journal of internal medicine. 2010 Jan;267(1):89-105
46. Anjum S, Ishaque S, Fatima H, Farooq W, Hano C, Abbasi BH, Anjum I. Emerging applications of nanotechnology in healthcare systems: Grand challenges and perspectives. Pharmaceuticals. 2021 Jul 21;14(8):707
47. Torres-Ortega PV, Saludas L, Hanafy AS, Garbayo E, Blanco-Prieto MJ. Micro-and

nanotechnology approaches to improve Parkinson's disease therapy. Journal of Controlled Release. 2019 Feb 10;295:201-13.
48. Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of Nanotechnology in Medical field. Global Health Journal. 2023 Feb 25
49. Sahoo BM, Kumar BV, Patra CN, Panda JR, Mohanta BC, Palei NN. Nanotechnology: a novel approach for drug development in health care system. Current Nanomaterials. 2020 Apr 1;5(1):12-25.
50. Patil M, Mehta DS, Guvva S. Future impact of nanotechnology on medicine and dentistry. J Indian Soc Periodontol 2008; 12(2): 34-40.
51. Italia JL, Bhatt DK, Bhardwaj V, Tikoo K, Kumar MN. PLGA nanoparticles for oral delivery of cyclosporine: nephrotoxicity and pharmacokinetic studies in comparison to Sandimmune Neoral. J Control Release 2007; 119(2): 197-206
52. N. Jedinger, J. Khinast, E. Roblegg, The design of controlled-release formulations resistant to alcohol-induced dose dumping – a review, Eur. J. Pharm. Biopharm. 87 (2014) 217–226,
53. Sharma, S., Rabbani, S. A., Agarwal, T., Baboota, S., Pottoo, F. H., & Kadian, R. (2021). Nanotechnology driven approaches for the management of Parkinson's disease: Current status and future perspectives. Current Drug Metabolism, 22(4), 287-298.
54. Li A, Tyson J, Patel S, Patel M, Katakam S, Mao X, He W. Emerging nanotechnology for treatment of Alzheimer's and Parkinson's disease. Frontiers in Bioengineering and Biotechnology. 2021:322.

HOW TO CITE: Mihir Parmar, Dev Gandhi, Deep Parekh, Hunedali Tinwala, Taufik Mulla, Nanotechnology In Parkinson's Disease, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 4, 105-139. https://doi.org/10.5281/zenodo.10953569