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Brain-Targeted Nano-Drug Delivery for the Treatment of Parkinson's Disease

Parkinson Hastalığının Tedavisi İçin Beyin Hedefli Nanoboyutlu İlaç Salımı

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ABSTRACT

Parkinson's Disease affects 2% to 3% of overall individuals aged 65 years or older worldwide and is considered to be the second most common age-related neurodegenerative disease. Neuropathologic features of Parkinson's Disease attributes to a loss of pigmented dopaminergic neurons in the substantia nigra and the formation of Lewy Bodies, as a result of intracellular accumulation of α-synuclein proteins. To our current day, only a few therapeutic approaches are considered promising, one of which is the Nanoscale approach. It gives an advantage over conventional approaches by offering solutions to complications that occur in the current treatment methods used for Parkinson's Disease, namely by encapsulating and protecting the drug from extracellular degradations, allowing for a more sustained, efficient, and targeted drug release profile, thus reducing the risk of adverse effects of the drug used. In this study, we review, discuss, and briefly explain the nanoscale approaches, alternative administration routes, and studies conducted *in vivo* and *in vitro* for an efficient treatment and an alternative approach to Parkinson's Disease.

Keywords: Blood–Brain Barrier, Nano-drug Delivery, Nanoparticles, Parkinson's Disease

ÖZ

Parkinson Hastalığı tüm dünyada 65 yaş ve üzeri bireylerin %2 ila %3'ünü etkilemektedir ve yaşa bağlı nörodejeneratif hastalıklar arasında ikinci en yaygın hastalık olarak kabul edilmektedir. Parkinson Hastalığının nöropatolojik özellikleri, Substantia nigra veya Kara maddede dopaminerjik nöronların kaybına ve α-sinüklein proteinlerinin hücre içi birikiminin bir sonucu olarak Lewy cisimciklerinin oluşumuna bağlanmaktadır. Günümüzde, sadece birkaç terapötik yaklaşımın umut verici olduğu düşünülmektedir ve bunlardan biri de nanoboyutlu yaklaşımdır. Parkinson Hastalığı için kullanılan mevcut tedavi yöntemlerinde ortaya çıkan komplikasyonlara çözümler sunarak, yani ilacı kapsülleyerek ve hücre dışı bozulmalardan koruyarak, sürekli, verimli ve hedeflenmiş bir ilaç salım profiline izin vererek ve böylece kullanılan ilacın yan etkilerini azaltarak geleneksel yaklaşımlara göre avantaj sağlar. Bu çalışmada, Parkinson Hastalığına etkin bir tedavi ve alternatif bir yaklaşım için nanoboyutlu yaklaşımlar, alternatif uygulama yolları ve *in vitro*/*in vivo* olarak yapılan çalışmalar gözden geçirilmekte, tartışılmakta ve kısaca açıklanmaktadır.

Keywords: Kan-Beyin Bariyeri, Nano İlaç Dağıtımı, Nanopartiküller, Parkinson Hastalığı

Introduction

Neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), are defined as disorders that affect the neural system and cause the degeneration of neurons in the brain. The degeneration stage is responsible for the resulting symptoms, starting with the gradual loss of memory and coordination leading to a full loss of function. As current treatments can only manage the symptoms, not the disorder progression, the attempts to discover effective ways to diagnose, treat, and slow these disorders are important. To overcome these outcomes of disorder, drugs or therapeutic agents are required to enter the central nervous system (CNS), in other words, these drugs must infiltrate the blood-brain barrier (BBB). While this is not an easy mission due to the structure and functional complexities of the BBB making the latter a major obstacle for drug delivery to CNS (Pardridge, 2005). The unique structure of BBB plays a major role in the passage of any solutes from the circular system to the brain, in detail, capillaries formed by the microvessel endothelial cells, low pinocytic potential, high amounts of enzymes, and tight intercellular junctions are all factors contributing to the permeability of the BBB. Furthermore, the comprehensive study of the

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BBB structure and full understanding of the disease will majorly enhance the detection of the disease and innovate the techniques used for circumvention and drug delivery to the brain and targeting the affected cells (Spector, 2000).

However, due to its complex nature, the vast diversity of genetic variation of the disease, and limited therapeutic approaches to the disease, treatment of PD has branched to the more personalized and molecular level. Genome editing technology offers to treat the disease by genetically modifying cells that are involved directly in the pathophysiology of the disease or modifying the genome of a cell that is indirectly involved with the disease however, can induce events to alleviate symptoms caused by the disease. Although, a comprehensive review article on current clinical trials on genome editing in PD by Arango, David, et al. indicated the limitations and challenges of genome editing technology and concluded that more research is still needed on account of several reasons (Arango et al., 2021). In recent years, the delivery of drugs and therapeutic agents through BBB to the brain has significantly improved with the discovery of Nanoparticles (NPs) and their ability to work as nanocarriers for drug delivery such as Polymeric, Lipids, or Metal NPs. The objective of these NPs is to carry the modified therapeutic agents to the brain to induce a positive effect in slowing the rate of the disease and its progression in the human CNS (Kabanov & Batrakova, 2005).

This presented review is to serve the outcome of providing an understanding of the essence of how brain-targeted nano-drug delivery for the treatment of PD works and the methods used. Our review is distinctly organized into several parts, starting with a summarized introduction to PD and the conventional therapeutic methods used in the modern day. Second, we elaborate on BBB and its structure and how NPs can be used to overcome this highly selective barrier to introduce an effective CNS disease treatment. Third, we introduce the main forms of NPs such as (Polymeric Nanospheres, Liposomes, Nanoemulsions (NEs), and Metal NPs) for the treatment of PD with their different structures and usages, demonstrating a promising future for disease detection and drug delivery to the brain. Fourth, we describe the administration routes of NPs in PD that showed significant results through conventional and unconventional routes. We finalize our review with a future perspective and conclusion discussing the possible promising technique for therapeutic repurposing against PD (Kabanov & Batrakova, 2005).

Neurodegenerative Diseases

Neurons are the building block of our nerves system and are indispensable for the efficient operation of the human brain as they are pivotal in facilitating communication and signaling between different regions of the brain. Their intricate network enables the transmission of vital information, contributing significantly to basic human processes such as learning, movement, body coordination, and memory retention.

While neurons, like other body cells, are not immortal, their gradual decline in number, along with alterations in neuron structure and function, constitutes a fundamental aspect of various brain disorders, a process termed neurodegeneration. This process underpins the pathophysiology of conditions known as neurodegenerative diseases which lead to debilitating symptoms and cognitive decline. Understanding the mechanisms driving neurodegeneration is crucial for developing effective treatments to mitigate its impact on brain function and overall well-being (Przedborski et al., 2003).

In a wider aspect, the name neurodegenerative disease represents the existence of unusual elements like abnormal protein misfolding in the neuron cells. These disorders affect various neuronal regions while separately influencing a distinct area of the brain. The precise reasons for the irregular folding and build-up of proteins are not fully comprehended yet. Evidently, neurological disorders are the result of disturbed immunity, age, genetics, and environment (Kabanov & Gendelman, 2007).

Central Nervous System

The CNS, which includes the brain and spinal cord, is critical for integrating information from many sensory modalities and coordinating a variety of complex functions in order to maintain homeostasis. The brain, the seat of consciousness and cognition, is divided into distinct regions, each with unique functions. The cerebrum, which makes up the majority of the brain, is in charge of sensory perception, voluntary motor activities, and higher cognitive processes including thinking, memory, and problem solving (Mukhtoraliyeva et al., 2024). The cerebellum, located at the rear of the brain, is responsible for muscular coordination and balance. The brainstem, which connects the brain and spinal cord, governs basic autonomic activities such as breathing, heart rate, and digestion. The midbrain, located within the brainstem, is a vital nexus in the CNS. The substantia nigra is located within its walls and is home to dopaminergic neurons that create dopamine, a neurotransmitter that is essential for many bodily functions. Functions of dopamine go beyond the regulation of voluntary movement to encompass aspects of reward, motivation, and emotional health (Enriquez-Traba et al., 2023).

A complex bundle of nerves extends from the brainstem down the spinal column, carrying impulses to and from peripheral tissues. Sensory neurons carry information from the body to the CNS, whereas motor neurons send orders from the CNS to muscles and glands, allowing for coordinated motions and reactions (Banerjee et al., 2023). The BBB protects the delicate architecture of the CNS by strictly regulating the movement of chemicals between the circulation and the brain. By understanding the nuanced interplay of neurotransmitters, neural circuits, and the protective mechanisms of the BBB, researchers aim to devise innovative strategies that enhance drug delivery precision, minimize side effects, and optimize therapeutic outcomes.

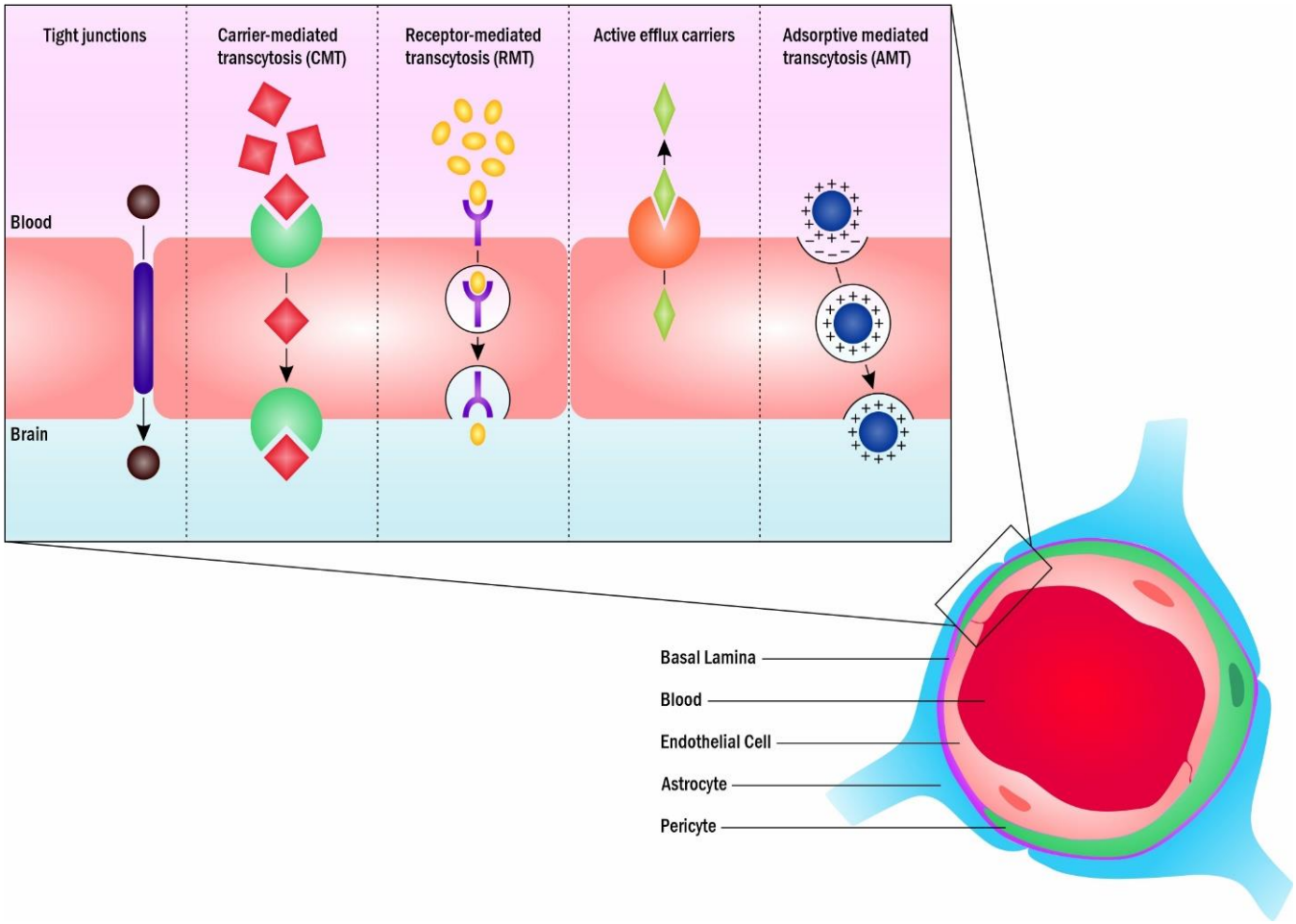

Figure 1: Structure and transport mechanism of Blood-brain Barrier: Endothelial cells, astrocyte end-feet covering the capillaries, and pericytes submerged inside the capillary basement membrane together forms BBB. There are passive and active pathways to cross the BBB: through tight junctions and transcytosis, which is the major method consisting of carrier-mediated transcytosis, receptor-mediated transcytosis, active efflux carriers, and adsorptive-mediated transcytosis.

Blood-Brain Barrier

The BBB is an extremely selective partially permeable wall of endothelial cells (EC) which prohibits pathogens in capillaries from passing non-selectively into the interstitial fluid of the CNS, where the neurons exist. EC, astrocyte end-feet covering the capillaries, and pericytes submerged inside the capillary basement membrane together contribute to the formation of the BBB. Fig. 1 illustrates the structure and transport mechanism of the BBB. This network enables the diffusion of certain small molecules, selective and active transport of ions, and biomolecules including sugars and proteins which are essential for brain functioning. This transportation occurs with the help of transport proteins that are specified for molecules. The barrier also prevents the entry of peripheral immunological components into the CNS, such as ligands, antibodies, and lymphocytes, therefore protecting the brain from harm caused by peripheral immune events (Li et al., 2018).

Many approaches have been suggested by using nanotechnology to pass BBB, especially with NPs. Several NPs have been used to overcome the selectivity of the BBB. The lipophilic properties of certain NPs allow them to pass the BBB and reach the nerve cells via a variety of alternative routes. There are passive and active pathways to cross the BBB; through tight junctions (Ding et al., 2020) and transcytosis, which is the major method consisting of active efflux carriers, carrier-mediated transcytosis, receptor-mediated transcytosis (RMT), and adsorptive mediated transcytosis (Zhou et al., 2018).

Furthermore, with the help of encapsulating ligands, NPs can target particular cells and move through the BBB from circulation via RMT (Pulgar, 2019). The NPs loaded with drugs can cross the BBB by passing through the tight junctions between the ECs. Drug transport across the EC wall can also be promoted by NP endocytosis and transcytosis (Saeedi et al., 2019). There are numerous receptors that are present on the BBB and have the ability to precisely interact with certain neurotransmitters and uptake them into cells. The transportation of such molecules through the BBB can be facilitated by the use of NPs. The most successful technique for delivering NPs to the neurons over the BBB has so far been RMT caused by the interplay of receptors and ligands. Specialized ligands like glycoproteins interact with the surface of NPs during the RMT (Sharma et al., 2019). This interaction is dependent on the membrane endothelial receptors. Alternative ligand chemicals, like lipoprotein, also can attach to certain receptors (Rhea & Banks, 2021)

Parkinson's Disease

PD affects 2% to 3% of overall individuals aged 65 years or older worldwide and is the second most common age-related neurodegenerative disease after AD, although depending on the environment, ethnicity, and race, the prevalence of PD varies (Poewe et al., 2017). For example, concerning environmental factors, the risk of PD is higher in individuals exposed to brain injuries or who have inhaled or ingested pesticides, and lower in caffeine and smoke users. In addition, the prevalence of incomplete penetrance genes such as LRRK2 and GBA, which encodes leucine-rich repeat serine/threonine-protein kinase 2 and glucocerebrosidase respectively, results in the increase of PD prevalence (Chillag-Talmor et al., 2011).

substantia nigra and the dopaminergic neurons in the midbrain with less severity compared to neurons in the substantia nigra. Additionally, α-synuclein proteins accumulate in neurons in the olfactory system and in monoaminergic and cholinergic brainstem neurons. However, by the end stage of PD, loss of the dopaminergic neurons is more widespread, and intracellular accumulation of α-synuclein proteins in neocortical and limbic regions is observed (Iacono et al., 2015). Fig. 2 describes the α-synuclein pathophysiology of PD and formation of LBs, illustrating the molecular and cellular mechanisms that contribute to the degeneration of dopaminergic neurons in the substantia nigra.

Genetic mutations in SNCA, VPS35 and LRRK2 are primary reasons behind autosomal-dominant form of PD while, loss of

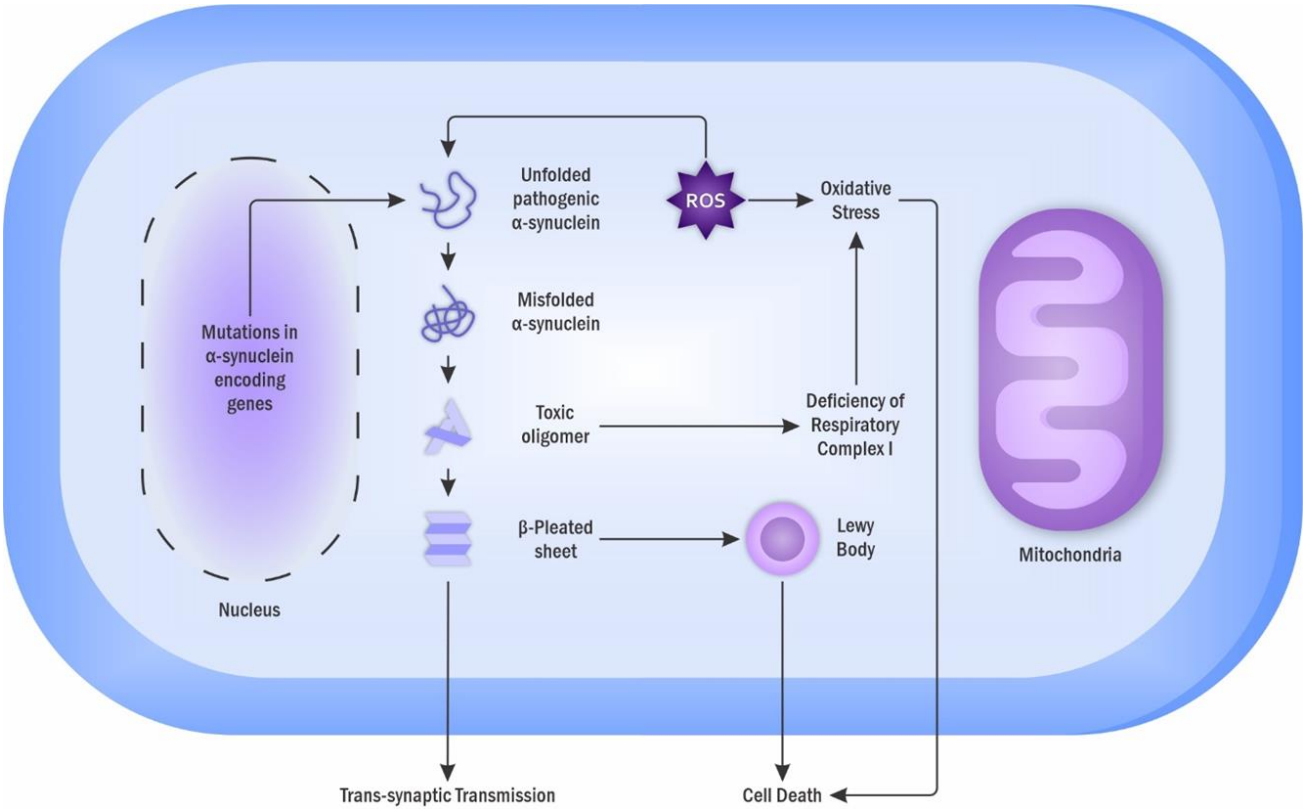

Figure 2: Cellular pathophysiology of Parkinson's disease

Neuropathologic features of PD are attributed to the loss of pigmented dopaminergic neurons in substantia nigra and the formation of Lewy bodies (LBs), as a result of intracellular accumulation of α-synuclein proteins. However, individually neither the intracellular accumulation of α-synuclein proteins nor the loss of pigmented dopaminergic neurons in substantia nigra is a specific attribute of PD, although together, these neuropathologic features are specific parameters for the diagnosis of idiopathic PD (Marsili et al., 2018). As the disease progresses, neuropathologic characteristics show abnormalities. In the earlier stages of PD, loss of pigmented dopaminergic neurons is exclusive in both the ventrolateral region of the

function mutations in PRKN, PINK1 and DJ-1 are mainly responsible for autosomal-recessive form of PD. In brief, SNCA encodes for a small protein called α-synuclein which has high expression profiles in pre-synaptic terminals of CNS. Though, it's function is mainly unknown, according to literature α-synuclein plays a role in neurotransmitter release and synaptic plasticity. Mutations in SNCA results α-synuclein to misfold and accumulate in intracellular space. VPS35 encodes for Vacuolar protein sorting-associated protein 35 which is one of the elements in the retromer complex. D620N pathogenic mutation in VPS35 induces the accumulation of α-synuclein proteins in dopaminergic neurons. LRRK2 encodes for Leucine-rich repeat serine/threonine-protein kinase 2. Multi-domain protein

encoded by this gene regulates intracellular protein trafficking and contains protein kinase and GTPase activities. G2019S pathogenic mutation in LRRK2 induces degeneration of dopaminergic neurons while several other mutations affect accumulation of α-synuclein proteins by preventing degradation. PRKN encodes for Parkin. Proteins encoded by this gene acts as a E3 ubiquitin ligase and regulates post-translational modifications of ubiquitin proteins and lysine residues. Mutations in PRKN account for the 77% of known cases in early onset of PD in individuals under the age of 30. PINK1 is located in human chromosome 1 and encodes for PTEN-induced protein kinase 1. Protein encoded by this gene acts alongside with Parkin by recruiting it to the site of damaged mitochondria and trigger mitophagy. Loss-of-function mutations in PINK1 affects the kinase domain of the protein and reduces the efficacy for mitophagy. DJ-1 encodes for Protein DJ-1. Protein encoded by this gene regulates oxidative stress of the neurons by acting as an antioxidant. Point and structural mutations in DJ-1 result in pathological oxidative stress and degradation of neurons. Pathological mutation in DJ-1 accounts for 1-2% of known cases in familial early onset of PD (Balestrino & Schapira, 2020).

As given in the previous paragraph, several proteins encoded by PD-related genes intervene in molecular pathways, particularly in mitochondrial function, oxidative stress, neuroinflammation, calcium homeostasis, α-synuclein proteostasis, and axonal transport, consequently accumulation of these proteins results in the sporadic PD-like neuropathology. Additionally, a genome-wide association study by Mike A. Nalls et al. indicated that several PD-related genes encoding for those proteins are also influenced in sporadic PD. Increased transcription of SNCA, a gene that encodes α-synuclein, results in mitochondrial accumulation in the deficiency of respiratory complex I and an increase in oxidative stress (Nalls et al., 2014).

Conventional Therapies in Parkinson's Disease

The underlying mechanism of cardinal motor degeneration in PD is a consequence of the loss of pigmented dopaminergic neurons in substantia nigra pars compacta, which then results in dopamine depletion in the striatum (Vekrellis et al., 2011). To substitute the dopamine depletion in the striatum, the regulation of dopaminergic transmission is maintained by the administration of certain drugs for the management of PD symptoms. Levodopa (L-DOPA) is a dopamine precursor used vastly in the management of PD; however, L-DOPA has low bioavailability and in order to obtain its stable effects, the dosage of this drug is increased, which results in the increase of its side effects. According to the study done *in vivo* by I.G. Kondrasheva et al, intranasal administration of L-DOPA conjugated PLGA (L-DOPA-PLGA) resulted in a 90±13% long-lasting and higher effect after 24 hours, moreover, after 4 weeks of administration, coordination of L-DOPA-PLGA treated rats were two times greater compared to naked administration of L-DOPA and L-DOPA+benserazide treated rats (Gambaryan et al., 2014).

New Approaches

As stated, conventional treatment approaches for PD are limited, and therapeutic agents only alleviate the symptoms that the disease causes, rather than preventing its progression. Moreover, these agents do not address non-dopamine-dependent attributes. With advancements in technology and a better understanding of the pathophysiology of PD, novel approaches are emerging. These aim to treat the disease by targeting its molecular, genetic, and cellular structures.

Immunotherapy

Cell to cell spread of α-synuclein aggregates directly induces the extracellular propagation of pathophysiology of the disease to healthy, adjacent dopaminergic neurons. As research by Shahnawaz et al. aims to identify the strains of α-synuclein that are responsible for the propagation of the aggregates, experimental approaches are aiming to prevent the cell-to-cell spread of α-synuclein aggregates (Shahnawaz et al., 2020). For instance, in order to degrade extracellular disease-propagating α-synuclein, antibodies have been utilized. According to research conducted by Fields et al. passive and active immunization techniques against α-synuclein have been demonstrated as neuroprotective agents in animal models, as well as in early clinical trials in humans (Fields et al., 2019).

Gene Therapy

Gene therapy is employed to correct, replace, or silence the gene of interest and offers advantages over conventional approaches to the disease, as minimal to no adverse effects are reported. In the treatment of PD, gene therapy is directed towards the disease by interacting with either disease-modifying or non-disease-modifying genes, and generally, the delivery of the sequence of interests is conducted by adeno-associated viruses or non-replicating viral vectors. Briefly, the disease-modifying approach aims to prevent the neurodegeneration caused by PD, while the latter aims to target the expression of dopaminergic enzymes. An article aiming to approach the disease by the latter, identified the genes and enzymes responsible for dopamine synthesis in neuronal cells (Nagatsu, 2023). The article further reported that reconstructing the diminished dopamine synthesis pathway in dopaminergic cells in the substantia nigra by introducing the genetic sequence of three enzymes responsible for dopamine synthesis was well tolerated by monkeys.

Cell Therapy

Over the decades, cell and tissue-based therapies were within the scope of interest. However, due to difficulties in standardization and adverse side effects, particularly stemming from the heterogeneous cell population present in tissue transplants, research has shifted towards homogeneous cell transplantation, consisting particularly of induced pluripotent stem cells. This shift occurred because replacing the lost cells with cell therapy lacked the disadvantages that tissue-based therapies

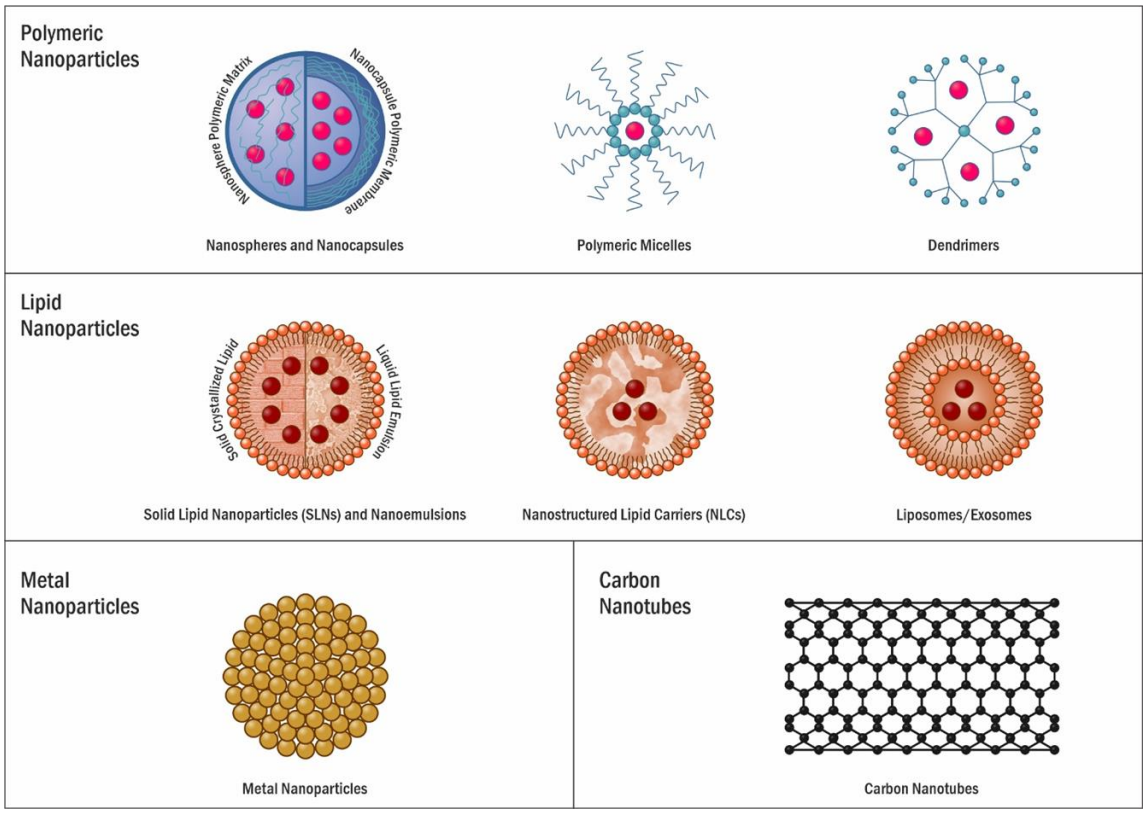

Figure 3: Nanoparticles used in the treatment of Parkinson's can be generally categorized as polymeric, lipids, metal NPs, and carbon nanotubes. Polymeric nanoparticles which are nanocapsules, nanospheres, dendrimers, and polymeric micelles, are mainly composed of either natural or artificial polymers. Solid lipid nanoparticles, liquid nanoemulsions, and an amorphous mixture of solid and liquid nanoparticles – nanostructured lipid carriers, liposomes, and exosomes are the main types of lipid nanoparticles.

had. Research conducted by Kikuchi et al. demonstrated that primates induced with Parkinson's disease, transplanted with dopaminergic progenitor cells derived from induced pluripotent stem cells, have survived, and functioned as dopaminergic neurons (Kikuchi et al., 2017). Furthermore, primates who received that cell therapy showed increased movement after transplantation.

Repurposing of Other Drugs

The process of finding new uses or applications for drugs that fall outside the scope of their original medical indications is referred to as drug repurposing. Rather than creating brand-new medications from the ground up, scientists investigate already-approved medications to discover new therapeutic applications, frequently for ailments other than those for which they were intended. Repurposing existing drugs can result in shorter development times and less expense spent than creating brand-new ones. For instance, an article by Stoker et al. reported that nilotinib, a tyrosine kinase inhibitor, has been repurposed and tested in patients with PD (Stoker et al., 2018). Since nilotinib is used to treat chronic myelogenous leukemia, and exenatide is an established treatment for type 2 diabetes mellitus, data on the safety and tolerability of these agents in patient populations were already available. Moreover, they also indicated that in mouse models with nigrostriatal degeneration, exenatide has been demonstrated to have neuroprotective and neurorestorative effects.

Nanoparticles for the Treatment of Parkinson's Disease

The recent advances in nanotechnology have shown that the utilization of NPs in the medical field holds great potential due to the numerous characterizations and properties such as shape, surface, size, and many others that can be harnessed to develop NPs as carriers of medications for treating and targeting various diseases. NPs have an impressive malleability allowing for the attachment of different biomolecules, resulting in safe and efficient transportation of pharmacologically active agents such as drugs. Due to their extremely small size (1-100nm), NPs can penetrate major physiological barriers such as the BBB (Venkatas & Singh, 2021). Many NPs have been employed in this matter, NPs can be generally categorized as polymeric, lipid, and inorganic NPs, as illustrated in fig. 3.

Polymeric Nanoparticles

With the two essential types being Nanocapsules and Nanospheres, the polymeric NPs are mainly composed of either natural or synthetic polymers. Furthermore, they are sorted into very specific structures that have proven the characteristics of biocompatibility, biodegradability, and non-toxicity. The Concept of Nanocapsules is that the drug is encapsulated in a polymeric vesicle. On the other hand, Nanospheres, where the drug is enclosed in a matrix of polymer or adsorbed onto its surface is degraded allowing flexibility in the rate of delivery reaching from

days to months (Łukasiewicz et al., 2021). In addition, more advanced polymeric structures such as Polymeric micelles and Dendrimers are explained in the following section.

Polymeric Nanospheres

Various types of synthetic polymeric nanospheres, generally, polyglycolic acid, polylactic acid, polyethylene glycol (PEG), poly(ε-caprolactone) (PCL), and Poly(lactic-co-glycolic acid) (PLGA) are employed regarding their biocompatibility, biodegradability and, modifiable surface structures such as ligands and proteins for site-specific deliveries and increased permeabilities from biological barriers (Castro et al., 2022).

According to the *in vivo* study by Yuying Zhao et al., oral administration of Ginkgolide B, which has an antioxidant and neuroprotective effect encapsulated PEG-PCL in MPTP, induced murine PD model resulted in more efficient uptake and accumulation of Ginkgolide B in both cerebral cortex and blood compared to naked oral administration of Ginkgolide B and concluded that encapsulation of Ginkgolide B with PEG-PCL has increased the efficacy of drug intake, achieved the more sustained release of the drug, and decreased the toxicity caused by Ginkgolide B (Y. Zhao et al., 2020). In another study conducted *in vivo* and *in vitro* by Kaili Hu et al, *in vitro* uptake of Lactoferrin conjugated PEG-PLGA (Lf-PEG-PLGA) resulted in more accumulation compared to unconjugated PEG-PLGA in bEnd. 3 cell line, moreover human-GDNF administration (IV) of urocortin incorporated Lf-PEG-PLGA resulted in 2.49 times of greater accumulation compared to urocortin incorporated unconjugated PEG-PLGA in 6-OHDA induced PD mouse model and included that urocortin incorporated Lf-PEG-PLGA decreased the striatum lesion induced by 6-OHDA *in vivo*, finally concluded that Lf-PEG-PLGA might be a promising therapeutic potential for PD (Hu et al., 2011).

Other than these synthetic polymeric examples, there are also natural polymers that are quite useful in drug delivery to the brain. The biggest example of these polymers is chitosan (CS). CS is a linear polymer that can be obtained from the chitin shells of crustaceans. The production of CS-NPs is a convenient strategy because of their biocompatibility and unique features, including positive charge, that allows for ionotropic gelation (Sahin et al., 2017). Md, Shadab et al. investigated whether bromocriptine-loaded CS-NPs can deliver therapeutic agents to the brain via a non-invasive nasal route, hence increasing bioavailability (Md et al., 2014). NP compositions did clearly reverse haloperidol-induced PD, according to a dopaminergic and histopathological analysis of murine brains. Such observations imply that the drug delivery method presented here might provide an efficient non-invasive way of promoting BRC entrance to the brain in clinical cases. Hernando et al. also made research to establish a unique NP, glial cell line-derived neurotrophic factor (GDNF) encapsulated in CS-coated Nanostructured Lipid Carriers (NLCs) modified with trans activator of transcription peptide (NLC-TAT-GDNF) for intranasal delivery to improve brain targeting in PD (Hernando et al., 2018). Motor recovery and modulation of microglia activation were observed in the CS-NLC-TAT-GDNF-treated cohort, which was verified by immunohistochemical tests. As a result, it is possible to infer that intranasal delivery of CS-NLC-TAT-GDNF could be a useful approach for PD treatment. There are many other studies about CS-NPs which have been successful and considered promising for PD.

Polymeric Micelles

Polymeric Micelles are dendrites considered as a form of complicated polymeric structures. These Polymeric micelles are composite of either natural or synthetic existing polymers and are structured in different ways. Polymeric micelles have demonstrated very promising characterizations that are essential for *in vivo* applications such as biocompatibility, biodegradability, and non-toxicity. Polymeric micelles are exceptionally well appropriate for drug delivery functions because they are characterized by nanoscopic core/shell configurations created by amphiphilic block copolymers, in addition to their inherent and modifiable characteristics especially for hydrophobic drugs. Inside the hydrophobic core of the polymeric micelles, the polymer chains have the ability to move in a way that allows significant amounts of the water-insoluble drug, reaching almost 50% of the micelle's weight without any major changes in the structure of the polymeric micelle (Alexander, 2018).

Wang, F. et al. state in their work that a poorly water-soluble non-ergoline dopamine agonist indicated for the treatment of PD called Rotigotine (ROT) has reached a (2.98 ± 0.92) mg/ml concentration and an absolute bioavailability of 84.6% which is a major increase compared to the conventional method of using ROT as PD treatment through IV of free ROT (F. Wang et al., 2020). In their conducted study, they have encapsulated ROT within the polymeric micelles so that it releases in a water-based thermosensitive gel after using the nasal route for administration in the rat model.

Dendrimers

Dendrimers are spherical polymers that are extremely branched and adjustable, produced by a sequence of organic coatings constructed on a smaller main component. These NPs are applied as possible nanocarriers of other functionally active pharmaceutical agents or as drugs themselves. Dendrimers have excellent biocompatibility and a hydrophilic outer layer, which make them useful in the nano-drug delivery field (Zhu et al., 2019). Poly(amidoamine) (PAMAM) dendrimers are an example of a flexible and repeatable form of NPs that may be loaded with drugs and changed by adding specific proteins which can target certain receptors (Abedi-Gaballu et al., 2018). Rekas et al. investigated the influence of PAMAM (G3, G4, and G5 generations) on α-synuclein fibrillation (Rekas et al., 2009). PAMAM dendrimers prevented a-synuclein fibrillation, and this activity grew relative to generation order and PAMAM content. PAMAM efficiently stimulated the breakdown of previous α-synuclein fibrils too. Because α-synuclein oligomers are thought to be cytotoxic, dendrimers, that induce amorphous aggregation

and limit the number of fibrils, may provide chances for a prophylactic strategy to the therapy of PD. Furthermore, phosphorus dendrimers can also inhibit α-synuclein fibrillation, nonetheless, their efficiency is dependent on the dendrimer amount and size. Lower amounts of phosphorus dendrimers were shown to suppress α-synuclein fibrils in several research studies (Ferrer-Lorente et al., 2021; Majoral et al., 2021).

Lipids

Due to their properties, lipid-based NPs are highly biocompatible. They can easily enter the CNS and bypass the first-pass metabolism of the body when absorbed through the lymphatic system. According to recent studies, lipid-based vesicles such as exosomes are an example, which is composed of phospholipids, and used to encapsulate drugs in PD model studies.

Solid Lipid Nanoparticles

Solid lipid NPs (SLNs) are globular NPs with an approximate diameter of 10 to 1000 nm that are utilized in innovative drug delivery mechanisms due to their high biodegradability (Duan et al., n.d.). A solid lipid inner structure in SLNs helps to dissolve lipid-soluble compounds. Surfactants (emulsifiers) help to keep the lipid center stable. SLNs are mainly used as nanocarriers for dopamine agents in the treatment of PD. Esposito et al. reported research for the production of a novel bromocriptine (BK) drug delivery mechanism, which is tested on PD hemilesioned rodents (Esposito et al., 2008). The tristearin-tricaprin mixture produced SLN with fixed sizes for up to six months after synthesis. Encapsulated BK was released in a protracted form for forty-eight hours with the help of Tristearin-tricaprin NPs. It is shown that encapsulating with SLN can be an efficient method for increasing the half-life of BK. Tsai et al. investigated the possibility of oral apomorphine (AP) administration via SLNs (Tsai et al., 2011). Glyceryl monostearate (GMS) and polyethylene glycol monostearate (PMS) have been used as emulsifying agents in SLNs. The *in vivo* drug dispersion data showed that SLNs effectively delivered AP to the brain striatum, significantly improving the potential of AP to cure PD. In a rodent model with PD, they discovered that the results of PMS outperformed GMS. Thus, oral delivery of AP from SLNs may be preferable over subcutaneous injection. To evade first-pass metabolism and increase efficiency in the treatment of PD, Pardeshi et al. examined intranasal administration of RP IV encapsulated in SLNs via the emulsification-solvent diffusion method (Pardeshi et al., 2013a). The findings indicated that the examined drug delivery mechanism might be seen as a potential option other than traditional tablet formulations. Leonardi et al. developed cationic SLNs for the ocular administration of Idebenone (IDE), an effective drug targeting mitochondrial dysfunction in PD (Leonardi et al., 2015). To assess the effect of NP coating on the antioxidant potential of IDE, an *in vitro* Oxygen Radical Absorbance Capacity test was conducted. The IDE-loaded SLNs produced in PBS demonstrated improved drug stability in contrast to the uncoated drug while retaining its *in vitro* antioxidant properties.

Nanostructured Lipid Carriers

NLCs are synthesized by mixing insoluble SLN and liquid NEs to form an amorphous solid mixture. NLCs are solid both in the body and at room temperature; therefore, have enhanced physical stability. The oil molecules in the mixture have no effect on the Solid Lipid' crystal matrix and crystals in SL don't dissolve in Liquid Lipids (LL) (Haider et al., 2020). Furthermore, LL incorporation into the matrix results in the formation of an amorphous lattice in the crystalline solid matrix of NLC; therefore, allowing more substance to be delivered. NLCs are classified with respect to their lipid content and divided into three groups, imperfect, amorphous, and multiple structures; hence synthesized accordingly. The size of NLCs generally ranges between 10 nm – 1000 nm and as surface area varies, the biocompatibility and drug release capacity of NLCs is affected (Üner, 2015). To enhance cellular uptake, the size of NLCs used to deliver chemotropic agents is suggested to be around 50 nm – 300 nm. The study done *in vivo* and *in vitro* by O. Gartziandia et al. indicated that daily intranasal administration of GDNF in CS-NLC-GDNF with a size of 130 nm was applied on 6-OHDA partially lesioned rat model and achieved behavioral improvements after 2 weeks and prevented 6-OHDO toxin to invade P12 cells. Furthermore, the *in vitro* findings concluded that CS-NLC-GDNF might be a therapeutic potential for PD (Gartziandia et al., 2015).

Nanoemulsions

NEs, also can be referred to as submicron emulsions, are stable isotropic systems in which immiscible liquids are made miscible to form a single-phase by the usage of surfactant or mix of surfactant with a co-surfactant (Nirale et al., 2020). NEs are mainly synthesized from generally regarded as safe pharmaceutical surfactants that can dissolve drugs with low solubility and prevent drugs from enzymatic degradation. NE globules contain negatively charged lipophilic and amorphous surfaces. Due to these properties, those globules can fuse with organisms containing lipid-based membranes and increase the efficacy of drug delivery while reducing the toxicity caused by it (McClements, 2021). A study done *in vivo* by Bharti Gaba et al. indicated that intranasal administration of physically stable Naringenin (NRG) NE incorporated with Vitamin E was successful to reverse grip strength, swimming activity, and muscle coordination induced by 6-OHDA in rats while increasing the efficacy of NRG to the brain by avoiding systemic circulation and protecting it from enzymatic degradation (Gaba et al., 2019). Another study done *in vivo* and *in vitro* by Gulam Mustafa et al. indicated that intranasal administration of thermodynamically stable NE incorporated with RP in the Wistar Rat brain resulted in notable translocation in the brain. The study concluded that intranasal administration of NE incorporated with RP has

therapeutic potential for the treatment of PD (Mustafa et al., 2012).

Liposomes

Liposomes are globular vesicles composed of one or more phospholipid bilayers that surround a watery center. They show remarkable drug delivery technology due to their nontoxicity and biodegradability. Liposomes have increased drug therapeutic potential by stabilizing chemicals, overcoming barriers to cellular and tissue absorption, and boosting drug distribution to specific areas *in vivo*, all while avoiding cytotoxic effects (Guimarães et al., 2021). Liposomes can be effectively loaded with active substances to bypass the BBB and increase the therapeutic efficacy of medications treating CNS-related diseases (Agrawal et al., 2017). Wang et al. investigated the preventive role of liposome-encapsulated resveratrol, a notable antioxidant, obtained from Polygonum cuspidatum on substantia nigra neurons of PD mice (Y. Wang et al., 2011). The findings demonstrate that after 2 weeks of liposome-encapsulated resveratrol treatment, the unusual rotary attitude, failure, and cell death of substantia nigra neurons, and overall Reactive Oxygen Species (ROS) levels were considerably reduced, while the antioxidative potential of nigral tissues was highly improved. However, resveratrol is liposome NPs that have a greater impact than basic resveratrol delivery. Kizelsztein et al. observed that Tempamine (TMN), a strong antioxidant, is effective in suppressing experimental autoimmune encephalomyelitis in rats when entrapped in the intraliposomal aqueous solution of pegylated nanoliposomes (nSSL) (Kizelsztein et al., 2009). Drug distribution tests of nSSL–TMN demonstrated that over 3% of the liposome-given amount entered the cortex of the encephalomyelitis rats. This aggregation inside the brain, together with the feature of TMN exhibits a regulated delayed release from the nSSL, which can indicate why nSSL–TMN has higher curative effectiveness over bare TMN. The findings imply that further research into nSSL–TMN for the treatment of PD against ROS is worthwhile.

Exosomes

Exosomes are extracellular membrane-bound vesicles with a wide range of compositions that participate in pathophysiological activities. Exosomes have been utilized as diagnostic indicators and possible drug delivery carriers due to their small size and ability to transport desired molecules to target tissues. Some features of exosomes include biocompatibility, favored tumor targeting, customizable addressing efficacy, and stability. Making them eye-catching and ideal for drug delivery systems in a variety of illnesses and cancer treatment (Patil et al., 2020). Zhao et al investigated the use of genetically engineered macrophages for actively targeted brain administration of GDNF (Y. Zhao et al., 2014). In PD rats, systemic injection of GDNF-expressing macrophages dramatically reduced degeneration and inflammation. Behavioral investigations verified the therapeutic potential of macrophage-based drug delivery systems. Another proposed medicinal method is the production of exosomes carrying the expressed neurotrophic factor, accompanied by effective GDNF transport to targeted cells. These combinations can act as a novel method relying on cell-mediated active administration of drugs that halt or prevent the course of PD, eventually providing a chance to individuals who already are severely afflicted by the condition. Furthermore, PEGylation studies have been conducted to test the distribution of medicine found in various drug delivery systems. Exosomes lacking PEG, operating as a drug-loaded NP delivery mechanism, demonstrated superior distribution, half-life, and possible capacity to penetrate the BBB, delivering their cargo to recipient cells (Batrakova & Kim, 2015; Haney et al., 2015). Exosomes also are implicated in the transportation of α -synuclein, which is essential for the development of PD.

Metallic Nanoparticles

In the presence of several important characterizations such as the physicochemical and biological compatibility in metals, such as Platinum, Gold, Silver, and Palladium, they have been recently utilized as materials for NP synthesis. For example, Gold NPs (AuNPs) are quite modifiable for the required purpose as they have been used before in many areas. Silver NPs (AgNPs), have demonstrated an adequate anti-viral and anti-microbial characteristic. There are also Bimetallic NPs which it is a composite of two different metals such as Au-Pd NPs, which are NPs tuned with Quercetin, holding the ability for induced autophagy in AD.

Gold Nanoparticles

AuNPs can be synthesized or modified by various types of methods regarding the required size, shape, and surface properties. Respective of their surface properties and area to be targeted, AuNPs can be conjugated with several types of substances or molecules such as antibodies, nucleic acid sequences, lipids, carbohydrates, and proteins (Pissuwan, 2017). In a review written by L. A. Dykman and N.G. Khlebtsov, the vast majority of AuNPs applied in biomedical applications are either spherical-shaped or rod-shaped particles (Dykman & Khlebtsov, 2011). Due to their differences in size and shape, AuNPs mentioned earlier exhibit unique cellular uptakes and optical properties which give rise to wide usage of AuNPs *in vitro* and *in vivo*. A Study done by Emily Córneo et al. indicated that applications of AuNPs (20nm) with 2.5mg/kg concentration for 5 consecutive days in 40 PD male mouse models significantly reduced the oxidative stress and moderately increased neurotrophic factors without toxicity (da Silva Córneo et al., 2020). Another study done by Jinwei Xue et al. indicated that AuNPs synthesized from the root extract of Paeonia Moutan applications of PM-AuNPs with 20μL/mL decreased the ROS generation levels of BV2 cells *in vitro* while *in vivo* PM-AuNPs has increased the dopamine levels in substantia nigra and motor coordination in PD mouse models (de Bem Silveira et al., 2021; Xue et al., 2019).

Silver Nanoparticles

Generally, AgNPs range between 1-100 nm in scale and exhibit bactericidal properties by binding to the cell wall when ionized. Resulting in cellular damage to bacteria (T. Galatage et al., 2021). Apart from this property, when AgNPs are introduced to mammalian cells, they can cause damage by binding to the DNA and thiol groups of proteins due to the release of Ag+ ions (Gonzalez-Carter et al., 2017). Moreover, resulting in damage to the cellular & mitochondrial membrane and mitochondrial respiratory chain, leading to the production of ROSs and even cell death by inducing intrinsic apoptosis at a high rate (Mao et al., 2018). According to the *in vitro* study done by Akira Onodera et al., cells were exposed to AgNPs with a size of 70 nm, and 1 nm with a concentration of 5 µL/mg for an hour, which increased the ROS production in mitochondria only after 5 minutes and concluded that ROS production levels were higher with respect to the surface area of AgNPs that were used (Onodera et al., 2015). Another study done by Gonzalez Carter et al. indicated that applications of citrate-capped AgNPs, in mouse microglial N9 cell line given that microglial cells are correlated to PD, has significantly decreased inflammation of microglial cells and lipopolysaccharide (LPS)-mediated ROS by intracellular Ag2S formation resulting from CSE-mediated H2S production (Gonzalez-Carter et al., 2017).

Carbon Nanotubes

Carbon nanotubes (CNTs) are defined as cylindrical hollow shapes created by the rolling of graphene, they are categorized depending on the number of walls forming the cylindrical shape as single-walled, double-walled, and multi-walled (Herholz, 2008). CNTs are equipped with various properties, but their large surface area, small size, and ability to carry chemicals are the most advantageous properties that are used in the drug delivery field (Mota & Esteves, 2007). In detail, by creating either Supramolecular assemblies or stable covalent bonds, CNTs are loaded (LPS)-mediated

CNTs are able to penetrate the cells and allow the delivery of the drug to the cell. Originally, CNTs are fundamentally hydrophobic thus, in most solvents and biological media they cannot diffuse equivalently, so the drug delivery process doesn't happen efficiently till they are improved by functionalization which enhances their biocompatibility and solubility (Sun et al., 2006).

A recent study by Z. Yang et al, demonstrated how they have modified single-walled carbon nanotubes (SWCNTs) into delivering drugs in a successful manner for the treatment of experimentally induced AD with adequate dosage (Z. Yang et al., 2010). The inability of neurons to synthesize Acetylcholine (ACh) and the constant decrease in this neurotransmitter of the cholinergic nervous system is the main cause of AD (Linhardt et al., 2008). The controlled drug delivery of ACh into the brain can relieve the caused symptoms in the patients such as dementia, but free ACh cannot enter the brain because of its strong polarities and ease of decomposition in blood. SWCNTs are considered very efficient for the delivery of ACh molecules because of their ability to penetrate the brain through nerve axons and the absorption of both organic and inorganic substances (Kane & Stroock, 2007). Moreover, the ACh molecule is composed of an acetyl group and a quaternary ammonium group, allowing SWCNTs to absorb it effectively. The evidential medical impacts on the experimentally induced AD showed that SWCNTs effectively carried ACh into the brain and made ACh levels higher than an AD patient, thus, acting again as a neurotransmitter (M. Zhao et al., 2001).

Administration Routes of Nanoparticles in Parkinson's Disease

Throughout recent studies and research, NPs have shown the ability to enhance drug delivery by the utilization of both conventional and unconventional administration routes, in the following section we discuss the administration routes and applied studies using these delivery methods.

Oral Delivery

Oral delivery is considered to be the most preferred method of drug administration that is easily self-administrated and is non-invasive like the IV route and doesn't need sterilization beforehand. Oral delivery is deemed very challenging when it comes to stabilizing a certain bioavailability and concentration levels of a drug due to the constantly changing gastrointestinal (GI) tract nature and its conditions such as pH variations, thickness, the structure of the mucus covering the interior of the stomach walls, and the numerous cell types accompanied with different physiological functions, these conditions form an obstacle in the way of sufficient drug delivery resulting in the need for innovative NP design (Date et al., 2016). Controlling both site and rate of absorption is essential for an adequate design of drug formulations, moreover, NPs such as liposomal drug forms are being investigated to increase the oral route absorption (Date et al., 2016). A study conducted by Tsai et al. demonstrated the usage of NP encapsulation of Apomorphine, which is a dopamine receptor agonist for the treatment of PD that is administered in a subcutaneous injection with high frequency due to low half-life, and because of quick degradation in the GI tract and first-pass effect, it has a very poor oral bioavailability (<2%) (Bolger, 2018; Tsai et al., 2011). They decided to develop SLNs to encapsulate apomorphine in order to reach the appropriate oral bioavailability and desired location targeting. With an entrapment rate of 90%, the NPs developed were able to withstand up to 21 days in storage following oral administration of SLNs to rats, it was noticed that the bioavailability has got significantly enhanced by roughly 12- to 13-fold in comparison with the NP-free control group. More specific findings have demonstrated that one dose of SLNs loaded with Apomorphine has had the outcome of a bioavailability of around 25%, on the

other hand, by only using an oral solution, a bioavailability of 2.1% was recorded. Furthermore, the developed oral SLNs have shown the ability to deliver the same quantities as in conventional treatment in the mice brains and a promising greater therapeutic effectiveness when evaluated to a conventional Apomorphine solution (Tsai et al., 2011). Thus, yielding these Apomorphine encapsulated NPs as a very promising solution for oral administration.

Intranasal Route

BBB poses a significant challenge in the administration of PD therapeutic agents. Due to this reason, intranasal delivery is proposed for the delivery of some PD drugs. The Olfactory and Trigeminal pathway of the nasal mucosa to CNS makes it a potential adsorption site for therapeutics with minimal invasiveness, preventing GI and first-pass disruption, as well as bypassing the BBB, therefore increasing bioavailability and efficacy of drugs to be delivered. Recent studies indicated that the administration of PD drugs by intranasal route showed a dense accumulation of drugs in CNS as well as less systemic toxicity due to the adverse effects of PD drugs (Silva et al., 2021). However, due to the enzymatic degradation and surface charge of PD drugs, naked administration of these therapeutic agents decreases the efficacy significantly, therefore nanocarriers with suitable properties are proposed (Su et al., 2020). According to a study done *in vivo* and *in vitro* by Chandrakantsing V. Pardeshi et al. *in vitro* permeability test through sheep mucosa of RP loaded polymeric hybrid NP - achieved 78.46% mucoadhesion and 61.34% RP diffusion, and *in vivo*, intranasal administration RP incorporated NP in PD mice model decreased shivering and immobility in compression to oral-administration of RP tablet (Pardeshi et al., 2013b).

Transdermal Route

Transdermal drug administration might allow for continuous delivery of drugs, improved patient outcomes, and transfer straight to the blood (Rabiei et al., 2020). Nevertheless, these mechanisms are still not completely evolved, and it is difficult for many chemicals to get through the epidermis. Numerous permeability indicators have been established (Chen et al., 2020). These solutions, unfortunately, are linked to epidermal toxicity concerns (Manatunga et al., 2020). Furthermore, transdermal drug delivery might have varying absorption rates between people based on the skin quality of patients, therefore guaranteeing a reduction in intraindividual variation is required (D. Yang et al., 2021).

When designing a transdermal approach, potential skin responses such as rashes, and irritations must be taken into account. In scientific cases, several Selegiline transdermal methods had a few adverse effects on the skin of participants (Fang et al., 2009). *İn vivo* investigations in rat models of PD revealed that transdermal administration had a greater therapeutic impact than standard pills (Azeem et al., 2012). SLNs encapsulated in hydrogels are regarded as a novel and unconventional strategy for increased transdermal administration (Souto et al., 2020). Dudhipala et al. conducted research to establish, improve, and analyze the pharmacokinetic and pharmacodynamic behavior of RP loaded SLNs systems consisting of hydrogel for enhanced delivery (Dudhipala & Gorre, 2020). The findings show that LNPs and associated hydrogel compositions can be used as an alternate delivery method for enhanced transdermal distribution of RP for the successful treatment of PD

Intravenous Route

IV administration route is an invasive method used to provide drugs and fluid replenishment that must be spread across the body, particularly when fast delivery is a requirement, which is accomplished by directly injecting the subject with the prescribed medication into their circular systems such as antibiotics, antifungals, and antinociceptive drugs, and cancer chemotherapeutics. IV is given in either two ways, Bolus, or Infusion. Furthermore, using the IV route for drug delivery provides the benefit of instant drug efficacy by avoiding the first-pass drug phenomenon, which occurs when a drug goes under metabolization at a particular place in the body, usually the liver, resulting in a lower concentration of the therapeutic agent upon reaching its receptor sites or the systemic circulation (Sultatos, 2007). Drugs that are inadequately absorbed by the GI tract can be administered intravenously, also the drugs that are extremely excruciating when administered intramuscularly or subcutaneously may show no troubles by the administration through the IV route (Bolger, 2018). In a study conducted by R. Huang et al., it was shown how neuroprotection was achieved in a rat model that has gone under a rotenone-induced chronic PD. They have accomplished this neuroprotection using NPs encapsulating human-GDNF with multiple intravenously administered doses and comparing it with a single-time IV administration. Their findings have demonstrated the difference in GDNF expression in relation to the time and number of Lf-modified NPs, where the multiple injections of Lf-modified NPs had shown higher GDNF expression than that of a single injection (Huang et al., 2010).

Future Perspective and Conclusion

The pathophysiology of PD remains a mystery, making it challenging to discover an effective treatment. This is partially due to the lack of a defined diagnosis for detecting the earliest pathogenic pathways and neurodegenerative features. At the moment, pharmacologic treatment begins whenever a patient experiences motor symptom. However, by the time motor symptoms occur, the vast majority of dopaminergic neurons have already been destroyed. This is a significant barrier for therapeutics seeking to improve neural function and prevent the progression of the disease. Present treatment approaches are primarily aimed at delaying and reversing motor symptoms. This treatment approach can improve the quality of an individual's life; however, these therapies decrease efficacy and cause adverse effects over time.

On the other hand, nanobiotechnology is developing as a very effective method for overcoming the limitations that conventional medicine currently faces. With the help of nano-drug delivery techniques, it is possible to make multifunctional NPs with the capability to preserve drugs from degradation by the peripheral immune system before supplying targeted and triggered release to CNS. The use of nano-drug delivery systems might improve sustained release, reduce adverse effects, lower doses, and boost the efficiency of PD medications. Therefore, NPs can be thought of as a promising technique for therapeutic repurposing against PD.

The integration of nanobiotechnology with neuroscience has great potential to achieve revolutionary treatment strategies for a wide range of CNS-related diseases, including PD. It is this integration that will help us find the idea that will end the progression of PD rather than mitigate it.

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References

Abedi-Gaballu, F., Dehghan, G., Ghaffari, M., Yekta, R., Abbaspour-Ravasjani, S., Baradaran, B., Ezzati Nazhad Dolatabadi, J., & Hamblin, M. R. (2018). PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. In *Applied Materials Today* (Vol. 12, pp. 177–190). Elsevier Ltd. https://doi.org/10.1016/j.apmt.2018.05.002

Agrawal, M., Ajazuddin, Tripathi, D. K., Saraf, S., Saraf, S., Antimisiaris, S. G., Mourtas, S., Hammarlund-Udenaes, M., & Alexander, A. (2017). Recent advancements in liposomes targeting strategies to cross blood-brain barrier (BBB) for the treatment of Alzheimer's disease. In *Journal of Controlled Release* (Vol. 260, pp. 61–77). Elsevier B.V. https://doi.org/10.1016/j.jconrel.2017.05.019

Alexander, K. (2018). Biomedical Applications of Nano-Sized Polymeric Micelles and Polyion Complexes. *Journal of Siberian Federal University. Biology*, *11*(2), 110–118. https://doi.org/10.17516/1997-1389-0053

Arango, D., Bittar, A., Esmeral, N. P., Ocasión, C., Muñoz-Camargo, C., Cruz, J. C., Reyes, L. H., & Bloch, N. I. (2021). Understanding the Potential of Genome Editing in Parkinson's Disease. *International Journal of Molecular Sciences 2021, Vol. 22, Page 9241*, *22*(17), 9241. https://doi.org/10.3390/IJMS22179241

Azeem, A., Talegaonkar, S., Negi, L. M., Ahmad, F. J., Khar, R. K., & Iqbal, Z. (2012). Oil based nanocarrier system for transdermal delivery of ropinirole: A mechanistic, pharmacokinetic and biochemical investigation. *International Journal of Pharmaceutics*, *422*(1–2), 436–444. https://doi.org/10.1016/j.ijpharm.2011.10.039

Balestrino, R., & Schapira, A. H. V. (2020). Parkinson disease. *European Journal of Neurology*, *27*(1), 27–42. https://doi.org/10.1111/ENE.14108

Banerjee, D., Das, P. K., & Mukherjee, J. (2023). Nervous System. *Textbook of Veterinary Physiology*, 265–293. https://doi.org/10.1007/978-981-19-9410-4_11

Batrakova, E. v., & Kim, M. S. (2015). Using exosomes, naturally-equipped nanocarriers, for drug delivery. *Journal of Controlled Release*, *219*, 396–405. https://doi.org/10.1016/j.jconrel.2015.07.030

Bolger, G. T. (2018). Routes of Drug Administration ☆. In *Reference Module in Biomedical Sciences*. Elsevier. https://doi.org/10.1016/B978-0-12-801238-3.11099-2

Braak, H., del Tredici, K., Rüb, U., de Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, *24*(2), 197–211. https://doi.org/10.1016/S0197-4580(02)00065-9

Castro, K. C. de, Costa, J. M., & Campos, M. G. N. (2022). Drug-loaded polymeric nanoparticles: a review. *International Journal of Polymeric Materials and Polymeric Biomaterials*, *71*(1), 1–13. https://doi.org/10.1080/00914037.2020.1798436

Chen, M., Quan, G., Sun, Y., Yang, D., Pan, X., & Wu, C. (2020). Nanoparticles-encapsulated polymeric microneedles for transdermal drug delivery. *Journal of Controlled Release*, *325*, 163–175. https://doi.org/10.1016/j.jconrel.2020.06.039

Chillag-Talmor, O., Giladi, N., Linn, S., Gurevich, T., El-Ad, B., Silverman, B., Friedman, N., & Peretz, C. (2011). Use of a refined drug tracer algorithm to estimate prevalence and incidence of Parkinson's disease in a large israeli population. *Journal of Parkinson's Disease*, *1*(1), 35–47. https://doi.org/10.3233/JPD-2011-11024

da Silva Córneo, E., de Bem Silveira, G., Scussel, R., Correa, M. E. A. B., da Silva Abel, J., Luiz, G. P., Feuser, P. E., Silveira, P. C. L., & Machado-de-Ávila, R. A. (2020). Effects of gold nanoparticles administration through behavioral and oxidative parameters in animal model of Parkinson's disease. *Colloids and Surfaces B: Biointerfaces*, *196*, 111302. https://doi.org/10.1016/j.colsurfb.2020.111302

Date, A. A., Hanes, J., & Ensign, L. M. (2016). Nanoparticles for oral delivery: Design, evaluation and state-of-the-art. *Journal of Controlled Release*, *240*, 504–526. https://doi.org/10.1016/j.jconrel.2016.06.016

de Bem Silveira, G., Muller, A. P., Machado-De-Ávila, R. A., & Silveira, P. C. L. (2021). Advance in the use of gold nanoparticles in the treatment of neurodegenerative diseases: New perspectives. In *Neural Regeneration Research* (Vol. 16, Issue 12, pp. 2425–2426).

Wolters Kluwer Medknow Publications. https://doi.org/10.4103/1673-5374.313040

Ding, S., Khan, A. I., Cai, X., Song, Y., Lyu, Z., Du, D., Dutta, P., & Lin, Y. (2020). Overcoming blood-brain barrier transport: Advances in nanoparticle-based drug delivery strategies. *Materials Today (Kidlington, England)*, *37*, 112. https://doi.org/10.1016/J.MATTOD.2020.02.001

Duan, Y., Dhar, A., Patel, C., Khimani, M., … S. N.-R., & 2020, undefined. (n.d.). A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *Pubs.Rsc.Org*. Retrieved July 13, 2022, from https://pubs.rsc.org/en/content/articlehtml/2020/ra/d0ra03491f

Dudhipala, N., & Gorre, T. (2020). Neuroprotective Effect of Ropinirole Lipid Nanoparticles Enriched Hydrogel for Parkinson's Disease: *İn vitro*, Ex Vivo, Pharmacokinetic and Pharmacodynamic Evaluation. *Pharmaceutics*, *12*(5), 448. https://doi.org/10.3390/pharmaceutics12050448

Dykman, L. A., & Khlebtsov, N. G. (2011). Gold Nanoparticles in Biology and Medicine: Recent Advances and Prospects. *Acta Naturae*, *3*(2), 34–55. https://doi.org/10.32607/20758251-2011-3-2-34-56

Enriquez-Traba, J., Yarur-Castillo, H. E., Flores, R. J., Weil, T., Roy, S., Usdin, T. B., LaGamma, C. T., Arenivar, M., Wang, H., Tsai, V. S., Moritz, A. E., Sibley, D. R., Moratalla, R., Freyberg, Z. Z., & Tejeda, H. A. (2023). Dissociable control of motivation and reinforcement by distinct ventral striatal dopamine receptors. *BioRxiv*, 2023.06.27.546539. https://doi.org/10.1101/2023.06.27.546539

Esposito, E., Fantin, M., Marti, M., Drechsler, M., Paccamiccio, L., Mariani, P., Sivieri, E., Lain, F., Menegatti, E., Morari, M., & Cortesi, R. (2008). Solid lipid nanoparticles as delivery systems for bromocriptine. *Pharmaceutical Research*, *25*(7), 1521–1530. https://doi.org/10.1007/s11095-007-9514-y

Fang, J. Y., Hung, C. F., Chi, C. H., & Chen, C. C. (2009). Transdermal permeation of selegiline from hydrogel-membrane drug delivery systems. *International Journal of Pharmaceutics*, *380*(1–2), 33–39. https://doi.org/10.1016/j.ijpharm.2009.06.025

Ferrer-Lorente, R., Lozano-Cruz, T., Fernández-Carasa, I., Miłowska, K., de La Mata, F. J., Bryszewska, M., Consiglio, A., Ortega, P., Gómez, R., & Raya, A. (2021). Cationic Carbosilane Dendrimers Prevent Abnormal α-Synuclein Accumulation in Parkinson's Disease Patient-Specific Dopamine Neurons. *Biomacromolecules*, *22*(11), 4582–4591. https://doi.org/10.1021/acs.biomac.1c00884

Fields, C. R., Bengoa-Vergniory, N., & Wade-Martins, R. (2019). Targeting Alpha-Synuclein as a Therapy for Parkinson's Disease. *Frontiers in Molecular Neuroscience*, *12*, 496177. https://doi.org/10.3389/FNMOL.2019.00299/BIBTEX

Gaba, B., Khan, T., Haider, M. F., Alam, T., Baboota, S., Parvez, S., & Ali, J. (2019). Vitamin E Loaded Naringenin Nanoemulsion via Intranasal Delivery for the Management of Oxidative Stress in a 6-OHDA Parkinson's Disease Model. *BioMed Research International*, *2019*. https://doi.org/10.1155/2019/2382563

Gambaryan, P. Y., Kondrasheva, I. G., Severin, E. S., Guseva, A. A., & Kamensky, A. A. (2014). Increasing the Effciency of Parkinson's Disease Treatment Using a poly(lactic-co-glycolic acid) (PLGA) Based L-DOPA Delivery System. *Experimental Neurobiology*, *23*(3), 246–252. https://doi.org/10.5607/en.2014.23.3.246

Gartziandia, O., Herran, E., Pedraz, J. L., Carro, E., Igartua, M., & Hernandez, R. M. (2015). Chitosan coated nanostructured lipid carriers for brain delivery of proteins by intranasal administration. *Colloids and Surfaces B: Biointerfaces*, *134*, 304–313. https://doi.org/10.1016/j.colsurfb.2015.06.054

Gonzalez-Carter, D. A., Leo, B. F., Ruenraroengsak, P., Chen, S., Goode, A. E., Theodorou, I. G., Chung, K. F., Carzaniga, R., Shaffer, M. S. P., Dexter, D. T., Ryan, M. P., & Porter, A. E. (2017). Silver nanoparticles reduce brain inflammation and related neurotoxicity through induction of H 2 S-synthesizing enzymes. *Scientific Reports*, *7*. https://doi.org/10.1038/srep42871

Guimarães, D., Cavaco-Paulo, A., & Nogueira, E. (2021). Design of liposomes as drug delivery system for therapeutic applications. In *International Journal of Pharmaceutics* (Vol. 601, p. 120571). Elsevier B.V. https://doi.org/10.1016/j.ijpharm.2021.120571

Haider, M., Abdin, S. M., Kamal, L., & Orive, G. (2020). Nanostructured Lipid Carriers for Delivery of Chemotherapeutics: A Review. *Pharmaceutics*, *12*(3), 288. https://doi.org/10.3390/pharmaceutics12030288

Haney, M. J., Klyachko, N. L., Zhao, Y., Gupta, R., Plotnikova, E. G., He, Z., Patel, T., Piroyan, A., Sokolsky, M., Kabanov, A. v., & Batrakova, E. v. (2015). Exosomes as drug delivery vehicles for Parkinson's disease therapy. *Journal of Controlled Release*, *207*, 18–30. https://doi.org/10.1016/j.jconrel.2015.03.033

Herholz, K. (2008). Acetylcholine esterase activity in mild cognitive impairment and Alzheimer's disease. In *European Journal of Nuclear Medicine and Molecular Imaging* (Vol. 35, Issue SUPPL. 1, pp. 25–29). Springer. https://doi.org/10.1007/s00259-007-0699-4

Hernando, S., Herran, E., Figueiro-Silva, J., Pedraz, J. L., Igartua, M., Carro, E., & Hernandez, R. M. (2018). Intranasal administration of TAT-conjugated lipid nanocarriers loading GDNF for Parkinson's disease. *Molecular Neurobiology*, *55*(1), 145–155. https://doi.org/10.1007/s12035-017-0728-7

Hu, K., Shi, Y., Jiang, W., Han, J., Huang, S., & Jiang, X. (2011). Lactoferrin conjugated PEG-PLGA nanoparticles for brain delivery: Preparation, characterization and efficacy in Parkinsons disease. *International Journal of Pharmaceutics*, *415*(1–2), 273–283. https://doi.org/10.1016/j.ijpharm.2011.05.062

Huang, R., Ke, W., Liu, Y., Wu, D., Feng, L., Jiang, C., & Pei, Y. (2010). Gene therapy using lactoferrin-modified nanoparticles in a rotenone-induced chronic Parkinson model. *Journal of the Neurological Sciences*, *290*(1–2), 123–130. https://doi.org/10.1016/j.jns.2009.09.032

Iacono, D., Geraci-Erck, M., Rabin, M. L., Adler, C. H., Serrano, G., Beach, T. G., & Kurlan, R. (2015). Parkinson disease and incidental Lewy body disease: Just a question of time? *Neurology*, *85*(19), 1670–1679. https://doi.org/10.1212/WNL.0000000000002102

Kabanov, A., & Batrakova, E. (2005). New Technologies for Drug Delivery Across the Blood Brain Barrier. *Current Pharmaceutical Design*, *10*(12), 1355–1363. https://doi.org/10.2174/1381612043384826

Kabanov, A. V., & Gendelman, H. E. (2007). Nanomedicine in the diagnosis and therapy of neurodegenerative disorders. In *Progress in Polymer Science (Oxford)* (Vol. 32, Issues 8–9, pp. 1054–1082). Pergamon. https://doi.org/10.1016/j.progpolymsci.2007.05.014

Kane, R. S., & Stroock, A. D. (2007). Nanobiotechnology: Protein-Nanomaterial Interactions. *Biotechnology Progress*, *23*(2), 316–319. https://doi.org/10.1021/bp060388n

Kikuchi, T., Morizane, A., Doi, D., Magotani, H., Onoe, H., Hayashi, T., Mizuma, H., Takara, S., Takahashi, R., Inoue, H., Morita, S., Yamamoto, M., Okita, K., Nakagawa, M., Parmar, M., & Takahashi, J. (2017). Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. *Nature*, *548*(7669), 592–596. https://doi.org/10.1038/NATURE23664

Kizelsztein, P., Ovadia, H., Garbuzenko, O., Sigal, A., & Barenholz, Y. (2009). Pegylated nanoliposomes remote-loaded with the antioxidant tempamine ameliorate experimental autoimmune

encephalomyelitis. *Journal of Neuroimmunology*, *213*(1–2), 20–25. https://doi.org/10.1016/j.jneuroim.2009.05.019

Leonardi, A., Crascí, L., Panico, A., & Pignatello, R. (2015). Antioxidant activity of idebenone-loaded neutral and cationic solid-lipid nanoparticles. *Pharmaceutical Development and Technology*, *20*(6), 716–723. https://doi.org/10.3109/10837450.2014.915572

Li, Y., Zhu, Z., Huang, T., Zhou, Y., Wang, X., Yang, L., Chen, Z., Yu, W., & Li, P. (2018). The peripheral immune response after stroke—A double edge sword for blood-brain barrier integrity. *CNS Neuroscience & Therapeutics*, *24*(12), 1115–1128. https://doi.org/10.1111/cns.13081

Linhardt, R., Murugesan, S., & Xie, J. (2008). Immobilization of Heparin: Approaches and Applications. *Current Topics in Medicinal Chemistry*, *8*(2), 80–100. https://doi.org/10.2174/156802608783378891

Łukasiewicz, S., Mikołajczyk, A., Błasiak, E., Fic, E., & Dziedzicka-Wasylewska, M. (2021). Polycaprolactone Nanoparticles as Promising Candidates for Nanocarriers in Novel Nanomedicines. *Pharmaceutics*, *13*(2), 191. https://doi.org/10.3390/pharmaceutics13020191

Majoral, J. P., Zablocka, M., Ciepluch, K., Milowska, K., Bryszewska, M., Shcharbin, D., Katir, N., el Kadib, A., Caminade, A. M., & Mignani, S. (2021). Hybrid phosphorus-viologen dendrimers as new soft nanoparticles: Design and properties. In *Organic Chemistry Frontiers* (Vol. 8, Issue 16, pp. 4607–4622). Royal Society of Chemistry. https://doi.org/10.1039/d1qo00511a

Manatunga, D. C., Godakanda, V. U., Herath, H. M. L. P. B., de Silva, R. M., Yeh, C.-Y., Chen, J.-Y., Akshitha de Silva, A. A., Rajapaksha, S., Nilmini, R., & Nalin de Silva, K. M. (2020). Nanofibrous cosmetic face mask for transdermal delivery of nano gold: synthesis, characterization, release and zebra fish employed toxicity studies. *Royal Society Open Science*, *7*(9), 201266. https://doi.org/10.1098/rsos.201266

Mao, B. H., Chen, Z. Y., Wang, Y. J., & Yan, S. J. (2018). Silver nanoparticles have lethal and sublethal adverse effects on development and longevity by inducing ROS-mediated stress responses. *Scientific Reports*, *8*(1), 1–16. https://doi.org/10.1038/s41598-018-20728-z

Marsili, L., Rizzo, G., & Colosimo, C. (2018). Diagnostic criteria for Parkinson's disease: From James Parkinson to the concept of prodromal disease. In *Frontiers in Neurology* (Vol. 9, Issue MAR). Frontiers Media S.A. https://doi.org/10.3389/fneur.2018.00156

McClements, D. J. (2021). Advances in edible nanoemulsions: Digestion, bioavailability, and potential toxicity. In *Progress in Lipid Research* (Vol. 81, p. 101081). Elsevier Ltd. https://doi.org/10.1016/j.plipres.2020.101081

Md, S., Haque, S., Fazil, M., Kumar, M., Baboota, S., Sahni, J. K., & Ali, J. (2014). Optimised nanoformulation of bromocriptine for direct nose-to-brain delivery: Biodistribution, pharmacokinetic and dopamine estimation by ultra-HPLC/mass spectrometry method. *Expert Opinion on Drug Delivery*, *11*(6), 827–842. https://doi.org/10.1517/17425247.2014.894504

Mota, J. P. B., & Esteves, I. A. A. C. (2007). Simplified gauge-cell method and its application to the study of capillary phase transition of propane in carbon nanotubes. *Adsorption*, *13*(1), 21–32. https://doi.org/10.1007/s10450-007-9006-8

Mukhtoraliyeva, S., Tukhtamurodova, Z., & Djuraeva, B. (2024). NERVOUS SYSTEM AND ITS MAIN FUNCTIONS. *Евразийский Журнал Медицинских и Естественных Наук*, *4*(1), 61–67. https://doi.org/10.5281/ZENODO.5884973

Mustafa, G., Baboota, S., Ahuja, A., & Ali, J. (2012). Formulation Development of Chitosan Coated Intra Nasal Ropinirole Nanoemulsion for Better Management Option of Parkinson: An *İn vitro* Ex Vivo Evaluation. *Current Nanoscience*, *8*(3), 348–360. https://doi.org/10.2174/157341312800620331

Nagatsu, T. (2023). Catecholamines and Parkinson's disease: tyrosine hydroxylase (TH) over tetrahydrobiopterin (BH4) and GTP cyclohydrolase I (GCH1) to cytokines, neuromelanin, and gene therapy: a historical overview. *Journal of Neural Transmission (Vienna, Austria : 1996)*. https://doi.org/10.1007/S00702-023-02673-Y

Nalls, M. A., Pankratz, N., Lill, C. M., Do, C. B., Hernandez, D. G., Saad, M., Destefano, A. L., Kara, E., Bras, J., Sharma, M., Schulte, C., Keller, M. F., Arepalli, S., Letson, C., Edsall, C., Stefansson, H., Liu, X., Pliner, H., Lee, J. H., … Ansorge, O. (2014). Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nature Genetics*, *46*(9), 989–993. https://doi.org/10.1038/ng.3043

Nirale, P., Paul, A., & Yadav, K. S. (2020). Nanoemulsions for targeting the neurodegenerative diseases: Alzheimer's, Parkinson's and Prion's. In *Life Sciences* (Vol. 245, p. 117394). Elsevier Inc. https://doi.org/10.1016/j.lfs.2020.117394

Onodera, A., Nishiumi, F., Kakiguchi, K., Tanaka, A., Tanabe, N., Honma, A., Yayama, K., Yoshioka, Y., Nakahira, K., Yonemura, S., Yanagihara, I., Tsutsumi, Y., & Kawai, Y. (2015). Short-term changes in intracellular ROS localisation after the silver nanoparticles exposure depending on particle size. *Toxicology Reports*, *2*, 574–579. https://doi.org/10.1016/j.toxrep.2015.03.004

Pardeshi, C. v, Rajput, P. v, Belgamwar, V. S., Tekade, A. R., & Surana, S. J. (2013a). Drug Delivery Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: application of factorial design approach Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: application of factorial design approach. *Drug Deliv*, *20*(1), 47–56. https://doi.org/10.3109/10717544.2012.752421

Pardeshi, C. v., Rajput, P. v., Belgamwar, V. S., Tekade, A. R., & Surana, S. J. (2013b). Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: application of factorial design approach. *Drug Delivery*, *20*(1), 47–56. https://doi.org/10.3109/10717544.2012.752421

Pardridge, W. M. (2005). The blood-brain barrier: Bottleneck in brain drug development. *NeuroRx*, *2*(1), 3–14. https://doi.org/10.1602/neurorx.2.1.3

Patil, S. M., Sawant, S. S., & Kunda, N. K. (2020). Exosomes as drug delivery systems: A brief overview and progress update. *European Journal of Pharmaceutics and Biopharmaceutics*, *154*, 259–269. https://doi.org/10.1016/j.ejpb.2020.07.026

Pissuwan, D. (2017). Monitoring and tracking metallic nanobiomaterials *in vivo*. In *Monitoring and Evaluation of Biomaterials and their Performance İn vivo* (pp. 135–149). Elsevier Inc. https://doi.org/10.1016/B978-0-08-100603-0.00007-9

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, *3*(1), 1–21. https://doi.org/10.1038/nrdp.2017.13

Przedborski, S., Vila, M., & Jackson-Lewis, V. (2003). Series Introduction: Neurodegeneration: What is it and where are we? *Journal of Clinical Investigation*, *111*(1), 3. https://doi.org/10.1172/JCI17522

Pulgar, V. M. (2019). Transcytosis to cross the blood brain barrier, new advancements and challenges. *Frontiers in Neuroscience*, *13*(JAN),

1019. https://doi.org/10.3389/fnins.2018.01019

Rabiei, M., Kashanian, S., Samavati, S. S., Jamasb, S., & McInnes, S. J. P. (2020). Nanomaterial and advanced technologies in transdermal drug delivery. In *Journal of Drug Targeting* (Vol. 28, Issue 4, pp. 356–367). Taylor and Francis Ltd. https://doi.org/10.1080/1061186X.2019.1693579

Rekas, A., Lo, V., Gadd, G. E., Cappai, R., & Yun, S. I. (2009). PAMAM Dendrimers as Potential Agents against Fibrillation of α - Synuclein, a Parkinson's Disease-Related Protein. *Macromolecular Bioscience*, *9*(3), 230–238. https://doi.org/10.1002/mabi.200800242

Rhea, E. M., & Banks, W. A. (2021). Interactions of Lipids, Lipoproteins, and Apolipoproteins with the Blood-Brain Barrier. In *Pharmaceutical Research* (Vol. 38, Issue 9, pp. 1469–1475). Springer. https://doi.org/10.1007/s11095-021-03098-6

Saeedi, M., Eslamifar, M., Khezri, K., & Dizaj, S. M. (2019). Applications of nanotechnology in drug delivery to the central nervous system. In *Biomedicine and Pharmacotherapy* (Vol. 111, pp. 666–675). Elsevier Masson SAS. https://doi.org/10.1016/j.biopha.2018.12.133

Sahin, A., Yoyen-Ermis, D., Caban-Toktas, S., Horzum, U., Aktas, Y., Couvreur, P., Esendagli, G., & Capan, Y. (2017). Evaluation of brain-targeted chitosan nanoparticles through blood–brain barrier cerebral microvessel endothelial cells. *Journal of Microencapsulation*, *34*(7), 659–666. https://doi.org/10.1080/02652048.2017.1375039

Shahnawaz, M., Mukherjee, A., Pritzkow, S., Mendez, N., Rabadia, P., Liu, X., Hu, B., Schmeichel, A., Singer, W., Wu, G., Tsai, A. L., Shirani, H., Nilsson, K. P. R., Low, P. A., & Soto, C. (2020). Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy. *Nature*, *578*(7794), 273–277. https://doi.org/10.1038/S41586-020-1984-7

Sharma, G., Sharma, A. R., Lee, S. S., Bhattacharya, M., Nam, J. S., & Chakraborty, C. (2019). Advances in nanocarriers enabled brain targeted drug delivery across blood brain barrier. In *International Journal of Pharmaceutics* (Vol. 559, pp. 360–372). Elsevier B.V. https://doi.org/10.1016/j.ijpharm.2019.01.056

Silva, S., Almeida, A. J., & Vale, N. (2021). Importance of nanoparticles for the delivery of antiparkinsonian drugs. *Pharmaceutics*, *13*(4). https://doi.org/10.3390/pharmaceutics13040508

Souto, E. B., Baldim, I., Oliveira, W. P., Rao, R., Yadav, N., Gama, F. M., & Mahant, S. (2020). SLN and NLC for topical, dermal, and transdermal drug delivery. In *Expert Opinion on Drug Delivery* (Vol. 17, Issue 3, pp. 357–377). Taylor and Francis Ltd. https://doi.org/10.1080/17425247.2020.1727883

Spector, R. (2000). Drug transport in the mammalian central nervous system: Multiple complex systems. A critical analysis and commentary. In *Pharmacology* (Vol. 60, Issue 2, pp. 58–73). S. Karger AG. https://doi.org/10.1159/000028349

Stoker, T. B., Torsney, K. M., & Barker, R. A. (2018). Emerging treatment approaches for Parkinson's disease. *Frontiers in Neuroscience*, *12*(OCT), 419092. https://doi.org/10.3389/FNINS.2018.00693/BIBTEX

Su, Y., Sun, B., Gao, X., Dong, X., Fu, L., Zhang, Y., Li, Z., Wang, Y., Jiang, H., & Han, B. (2020). Intranasal Delivery of Targeted Nanoparticles Loaded With miR-132 to Brain for the Treatment of Neurodegenerative Diseases. *Frontiers in Pharmacology*, *11*, 1165. https://doi.org/10.3389/fphar.2020.01165

Sultatos, L. (2007). First-pass effect. In *xPharm: The Comprehensive Pharmacology Reference* (pp. 1–2). Elsevier Inc. https://doi.org/10.1016/B978-008055232-3.60022-4

Sun, M. L., Cheng, R. M., Xu, X. C., Chen, Y. W., & Li, M. G. (2006). Studies on adsorption of phenol and substituted phenols on carbon nanotubes. *Chemical Research and Application*, 18(1), 13.

Galatage, S. T., Hebalkar, A. S., Dhobale, S. V., Mali, O. R., Kumbhar, P. S., Nikade, S. V., & Killedar, S. G. (2021). Silver nanoparticles: properties, synthesis, characterization, applications and future trends. Silver micro-nanoparticles—Properties, synthesis, characterization, and applications. *IntechOpen*. https://doi.org/10.5772/intechopen.99173

Teleanu, D., Chircov, C., Grumezescu, A., Volceanov, A., & Teleanu, R. (2018). Blood-Brain Delivery Methods Using Nanotechnology. *Pharmaceutics*, *10*(4), 269. https://doi.org/10.3390/pharmaceutics10040269

Tsai, M. J., Huang, Y. bin, Wu, P. C., Fu, Y. S., Kao, Y. R., Fang, J. Y., & Tsai, Y. H. (2011). Oral apomorphine delivery from solid lipid nanoparticleswith different monostearate emulsifiers: Pharmacokinetic and behavioral evaluations. *Journal of Pharmaceutical Sciences*, *100*(2), 547–557. https://doi.org/10.1002/jps.22285

Üner, M. (2015). Characterization and imaging of solid lipid nanoparticles and nanostructured lipid carriers. In *Handbook of Nanoparticles* (pp. 117–141). Springer International Publishing. https://doi.org/10.1007/978-3-319-15338-4_3

Vekrellis, K., Xilouri, M., Emmanouilidou, E., Rideout, H. J., & Stefanis, L. (2011). Pathological roles of α-synuclein in neurological disorders. In *The Lancet Neurology* (Vol. 10, Issue 11, pp. 1015–1025). Elsevier. https://doi.org/10.1016/S1474-4422(11)70213-7

Venkatas, J., & Singh, M. (2021). Nanomedicine-mediated optimization of immunotherapeutic approaches in cervical cancer. *Nanomedicine*, *16*(15), 1311–1328. https://doi.org/10.2217/nnm-2021-0044

von Roemeling, C., Jiang, W., Chan, C. K., Weissman, I. L., & Kim, B. Y. S. (2017). Breaking Down the Barriers to Precision Cancer Nanomedicine. In *Trends in Biotechnology* (Vol. 35, Issue 2, pp. 159–171). Elsevier Ltd. https://doi.org/10.1016/j.tibtech.2016.07.006

Wang, F., Yang, Z., Liu, M., Tao, Y., Li, Z., Wu, Z., & Gui, S. (2020). Facile nose-to-brain delivery of rotigotine-loaded polymer micelles thermosensitive hydrogels: *İn vitro* characterization and *in vivo* behavior study. *International Journal of Pharmaceutics*, *577*, 119046. https://doi.org/10.1016/j.ijpharm.2020.119046

Wang, Y., Xu, H., Fu, Q., Ma, R., & Xiang, J. (2011). Protective effect of resveratrol derived from Polygonum cuspidatum and its liposomal form on nigral cells in Parkinsonian rats. *Journal of the Neurological Sciences*, *304*(1–2), 29–34. https://doi.org/10.1016/j.jns.2011.02.025

Xue, J., Liu, T., Liu, Y., Jiang, Y., Seshadri, V. D. D., Mohan, S. K., & Ling, L. (2019). Neuroprotective effect of biosynthesised gold nanoparticles synthesised from root extract of Paeonia moutan against Parkinson disease – *İn vitro* & *İn vivo* model. *Journal of Photochemistry and Photobiology B: Biology*, *200*, 111635. https://doi.org/10.1016/j.jphotobiol.2019.111635

Yang, D., Chen, M., Sun, Y., Jin, Y., Lu, C., Pan, X., Quan, G., & Wu, C. (2021). Microneedle-mediated transdermal drug delivery for treating diverse skin diseases. In *Acta Biomaterialia* (Vol. 121, pp. 119–133). Acta Materialia Inc. https://doi.org/10.1016/j.actbio.2020.12.004

Yang, Z., Zhang, Y., Yang, Y., Sun, L., Han, D., Li, H., & Wang, C. (2010). Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer disease. *Nanomedicine: Nanotechnology, Biology, and Medicine*, *6*(3), 427–441. https://doi.org/10.1016/j.nano.2009.11.007

Zhao, M., Brunk, U. T., & Eaton, J. W. (2001). Delayed oxidant-induced cell death involves activation of phospholipase A2. *FEBS Letters*, *509*(3), 399–404. https://doi.org/10.1016/S0014-5793(01)03184-2

Zhao, Y., Haney, M. J., Gupta, R., Bohnsack, J. P., He, Z., Kabanov, A. v., & Batrakova, E. v. (2014). GDNF-Transfected Macrophages Produce Potent Neuroprotective Effects in Parkinson's Disease Mouse Model. *PLoS ONE*, *9*(9), e106867. https://doi.org/10.1371/journal.pone.0106867

Zhao, Y., Xiong, S., Liu, P., Liu, W., Wang, Q., Liu, Y., Tan, H., Chen, X., Shi, X., Wang, Q., & Chen, T. (2020). Polymeric nanoparticles-based brain delivery with improved therapeutic efficacy of ginkgolide b in parkinson's disease. *International Journal of Nanomedicine*, *15*, 10453–10467. https://doi.org/10.2147/IJN.S272831

Zhou, Y., Peng, Z., Seven, E. S., & Leblanc, R. M. (2018). Crossing the blood-brain barrier with nanoparticles. *Journal of Controlled Release*, *270*, 290–303. https://doi.org/10.1016/J.JCONREL.2017.12.015

Zhu, Y., Liu, C., & Pang, Z. (2019). Dendrimer-Based Drug Delivery Systems for Brain Targeting. *Biomolecules*, *9*(12), 790. https://doi.org/10.3390/biom9120790