A Review on Nanoparticles for the Treatment in Parkinson's Disease

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ABSTRACT

Parkinson's disease is the second most common progressive neurodegenerative disease that promotes neuronal cell death. The primary treatment strategy for Parkinson's disease involves the therapy of an MAO-B inhibitor molecule. Nanotechnology refers to the creation and utilization of materials whose constituents exist at the nanoscale; and, by convention, be up to 100 nm in size. Nanotechnology explores electrical, optical, and magnetic activity as well as structural behavior at the molecular and submolecular level. It has the potential to revolutionize a series of medical and biotechnology tools and procedures so that they are portable, cheaper, safer, and easier to administer. Nanoparticles show very high mechanical properties as well as many remarkable physical properties. Their reactivity, durability and different properties are additionally reliant upon their novel size, shape and construction; there is appropriate possibility for different business and homegrown applications, which incorporate catalysis, imaging, clinical applications, energy-based examination, and ecological applications. Alzheimer's disease (AD) is a neurodegenerative disorder for which the research of new treatments is highly challenging. Since the fibrillogenesis of amyloid-β peptide 1–42 ($A\beta_{1-42}$) peptide is considered as a major cause of neuronal degeneration, specific interest has been focused on aromatic molecules for targeting this peptide.

Keywords: Nano particles, Parkinson’s disease, administration, Blood brain barrier (BBB).

INTRODUCTION:

A nanoparticle or ultrafine particle is usually defined as a particle of matter that is between 1 and 100 nanometres (nm) in diameter. Nanoparticles occur naturally, and can also be manufactured. Nanoparticles have many potential advantages, including increased strength and durability, improved electrical conductivity, and enhanced catalytic activity. They can also be used in targeted drug delivery, as well as in the development of more efficient solar cells and batteries.

A recent report from the World Health Organization shows that over 1.5 billion people worldwide are currently affected by neurological disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), stroke, headache, brain injuries, epilepsy, neuro infection, and multiple sclerosis [1,2,3,4]. Neurodegenerative diseases are conditions that affect the functioning of neurons in the brain by fluctuations in neurological functions [5,6]. Parkinson's disease (PD), a slowly progressive neurodegenerative disorder [7,8] characterized by bradykinesia associated with tremor, muscular rigidity and postural instability [9,10]. It affects 7–10 million people worldwide and typically in people over the age of 60 [11,12].

Selegiline nanoparticles are also used in the treatment of Parkinson’s disease. Although the mechanisms for selegiline’s beneficial action in the treatment of Parkinson’s disease are not fully understood, the selective, irreversible inhibition of monoamine oxidase type B (MAO-B) is thought to be of primary importance. MAO-B is involved in the oxidative deamination of dopamine in the brain. Selegiline binds to MAO-B within the nigrostriatal pathways (a bilateral dopaminergic pathway in the brain that connects the substantia nigra pars compacta (SNc) in the midbrain with the dorsal striatum (i.e., the caudate nucleus and putamen) in the forebrain) in the central nervous system, thus blocking microsomal metabolism of dopamine and enhancing the dopaminergic activity in the substantial nigra. Selegiline may also increase dopaminergic activity through mechanisms other than inhibition of MAO-B. At higher doses, selegiline can also inhibit monozmine oxidase type A (MAO-A), allowing it to be used for the treatment of depression. Dopamine is an essential chemical that occurs in many parts of the body. It is the premature degradation of dopamine that results in the symptoms of Parkinson’s disease. Monoamine oxidase (MAO) is an enzyme which accelerates the breakdown of dopamine[13]. Selegiline can prolong the effects of dopamine in the brain by preventing its breakdown through seletively blocking MAO-B. It also may prevent the removal of

dopamine between nerve endings and enhance release of dopamine from nerve cells.

The oral daily dose approved for the management of Parkinson's disease is 5–10 mg. However, for parenteral and transdermal routes, some studies have found that a lower dosage (1.5 mg–5 mg) is sufficient for the same amount of efficacy, which may also benefit in reducing side effects with reduced dosage delivered [14,15]. Patients taking high doses or regular doses of 5 mg–10 mg may experience psychiatric (agitations, delirium, hallucinations), cardiovascular (orthostatic, arterial hypertension) and neurological (sedation and abnormal movements) side effects [16]. Though Selegiline has beneficial effects in the brain regions, however, studies based on brain targeting of selegiline are limited [17] due to its hydrophilic nature which makes it difficult to cross blood brain barrier (BBB). But for the treatment of Parkinson's disease, achieving high drug concentration in the brain region is the main requisite. For such drugs polymeric nanoparticles (NPs) appears to be a new approach for drug delivery [18,19] due to their ability to deliver drugs having solubility problems to the target areas more precisely by penetrating through biological barriers such as BBB [20].

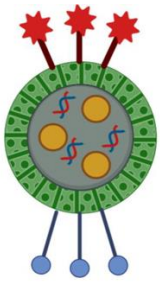
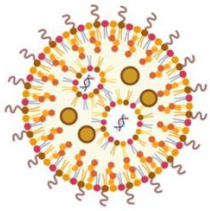
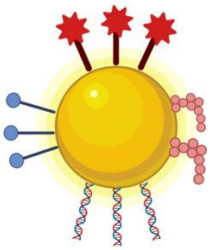
Nano formulations are widely used in drug formulation due to their numerous advantages, including safe and efficient delivery to specific areas. The most challenging aspect of delivering drug-loaded nanoparticles to the CNS is getting the drug across the BBB. Numerous factors of the nanoformulations such as density, size, targeted release, surface properties and physical-chemical properties make them a suitable candidate for crossing the BBB. Though various routes of administration are available for drug delivery such as intravenous (i.v), oral and nasal route, but their CNS targeting efficiency depend on the capacity to cross BBB effectively [21,22]. Intravenous administration of NPs causes their rapid access to bloodstream [23] but it is very irritating and not feasible for routine treatment in elderly patients. Similarly, nasal administration of NPs can act as a direct pathway for non-invasive NPs entry into the CNS bypassing BBB [24,25] but intranasal administration has very low residence time of drug in the nasal cavity to remain available for absorption.

Oral administration of NPs have advantage of non-invasive self-administration along with avoidance of any pain and discomfort associated with i.v. And nasal route but this route is not feasible for drugs which show poor intestinal absorption, instability, poor solubility, poor bioavailability or high-degree first-pass hepatic effects [26,27]. For such instances, transdermal films are nowadays evolved as alternative, non-invasive, self-administrable drug delivery system having advantage of improved bioavailability along with avoidance of hepatic first-pass metabolism.

The standard oral capsule formulation of selegiline hydrochloride under the trade name Eldepryl® is converted into an amphetamine metabolite causing confusion and jitteriness like side effects in the body[28,29]. Due to its low bioavailability freeze-dried tablet Zelapar® having oral disintegration with buccal absorption was designed. The tablets are convenient for patients who struggle to gulp down medication. Zelapar® increases drug delivery and decreases the formation of amphetamine byproduct by preventing first pass metabolism. An additional benefit of pre-gastric path results in minimize dosage since 1.25 mg of oral disintegrating tablet shows almost identical plasma concentration as 10 mg of a standard oral tablet. Alike other drug therapies for parkinson's disease oral disintegrating tablet also comes with adverse effects like headache, hallucinations, and dyspepsia along with with dizziness[30,31]. Several nanoformulations have been formulated and evaluated with the goal to reduce oxidative stress as well as upregulation of dopamine in parkinson's disease patients using different administration route, such as nanoemulsion [32,33], transdermal nanoemulgel [34,35] nanoparticles encapsulated transdermal film,etc.

The oral route being the most preferred route of administration needs to be explored for new and more intelligent drug delivery systems. Nanotechnology has been proposed to play a promising role in reversing the progression of the disease via the oral route[36,37,38]. Nanocarriers, namely nanoparticles, lipid nanoparticles, nanoemulsions, nanocrystals, nanomicellar formulations, self-nanoemulsifying drug delivery systems and alginate nanocomposites have been investigated upon to modulate the fate of drugs inside the human body when administered orally.

Advantages and disadvantages of nanoparticles

Polymeric nanoparticles	Lipid-based nanoparticles	Inorganic nanoparticles
Advantages • Biodegradable • Adjustable surface modifications • Use for hydrophilic and hydrophobic cargo **Limitations** • Self-aggregation may impact brain delivery	**Advantages** • Use for hydrophilic and lipophilic cargo • Ease of ligand conjugation to improve blood circulation **Limitations** • Potential cytotoxicity caused by non-specific uptake	**Advantages** • Small size • Increased uptake due to ionic interaction with BBB **Limitations** • Potential toxicity due to the metal accumulation

Figure 1: Advantages and Disadvantages of different types of nano particles

Method of preparation

Free nanoparticles are formed through either the breaking down of larger particles or by controlled assembly processes. Nanoparticles can be synthesized by few methods like Attrition, Pyrolysis and liquid phase synthesis methods like Solvothermal Methods (e.g. hydrothermal), Sol-Gel Methods, Synthesis in Structure Media (e.g., microemulsion).

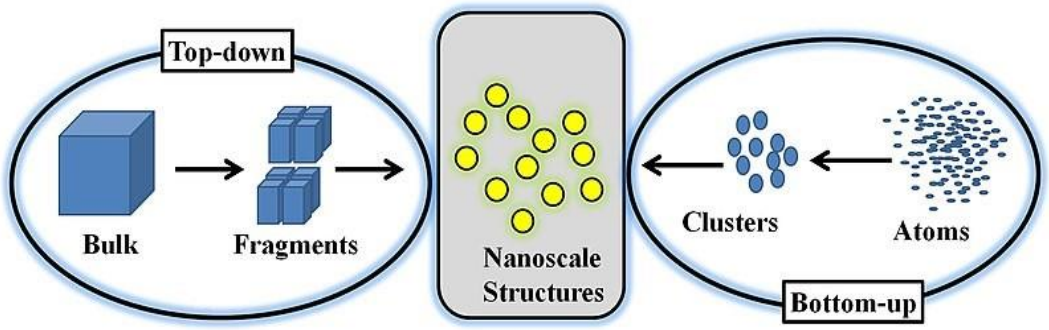


Figure 2: synthesis of nanoparticles in Attrition and Pyrolysis

Methods of synthesis of nanoparticles

There are three kinds of approaches for the production of nanoparticles.

A. Physical methods
B. Chemical methods
C. Biological methods

A. Physical methods

1. Mechanical Method
2. Pulse Laser Ablation
3. Pulsed Wire Discharge Method
4. Chemical Vapor Deposition
5. Laser Pyrolysis
6. Ionized Cluster Beam Deposition

B. Chemical methods

1. Sol-gel method
2. Sonochemical synthesis
3. Co-precipitation method
4. Inert gas condensation method
5. Hydrothermal synthesis

C. Biological methods

1. Synthesis using microorganisms
2. Synthesis using plant extracts
3. Synthesis using algae

Factors affecting the synthesis of nanoparticles–

- Temperature
- Pressure
- Time
- Particle size and shape
- Cost of preparation
- Pore size

Marketed drugs

Table 1: List of Marketed drugs

Drug	Description	Trade name
Piribedil	Piribedil is an antiparkinsonian agent, prescribed for Parkinson's disease, dizziness, and circulatory disorders.	Trivastal L.A.
Amantadine	Amantadine is a synthetic (man-made) anti-viral and antiparkinson agent, prescribed for Parkinson's disease and also for treating certain types of flu.	Comantrel Amantrel Neaman
Bromocriptine	Bromocriptine is a dopamine agonist, prescribed for Parkinson's disease either alone or with other medications.	Ovucript 2.5mg Briptin Bromotin Bromorex Criptal Bromogen B -Crip Semi Brom Sicriptin
Carbidopa-Levodopa	Carbidopa-Levodopa contains antidyskinetic drugs, prescribed for Parkinson's disease.	Tidomet LS Syndopa (110mg) Pardopa 110mg Duodopa (100 mg) Tidomet Plus Pardopa (125 mg) LCD (125) Parkimet(125mg) Neocare
Ropinirole	Ropinirole is a dopamine agonist, prescribed for Parkinson's disease and restless leg syndrome (RLS).	Ropeway(0.5mg) Ropin (0.5 mg) Parkirop (1 mg) Ropark (0.5 mg)
Selegiline	Selegiline is a selective and irreversible monoamine oxidase inhibitor (MAOI), prescribed for	Eldepryl (10 mg) Selerin Selgin

	Parkinson's disease either alone or with levodopa as an adjuvant.	Elegelin Jumex (5mg) Zelapar
Procyclidine	Procyclidine is an anticholinergic agent, prescribed for parkinsonism, Parkinson's disease, and drug-induced extrapyramidal syndrome.	Sycline (2.5mg) Axeps (2.5mg) Prodine (2.5mg) Parklid (2.5mg) Axeps (5mg) Kemadrin (2.5mg) Sycline (5mg) Parklid (5mg) Proly (5mg) Prodine (5mg)

CONCLUSION

Parkinson's disease is the second most common neurodegenerative disorder in the sexagenarian (a person who is between 60 and 69 years old) population. Parkinson's disease has a significant influence on treatment of patients and huge economic consequences. In the search for novel therapies for Parkinson's disease, noninvasive and biodegradable therapeutic treatments is needed. Nanocarriers should have the ability to cross the BBB, high drug loading, sustained release and targeting performance. Thus, we described diverse nanomaterials that possess the characteristics for an excellent delivery system. Nanoparticles can be used for early imaging of neuronal loss and nanodevices can help in the detection/quantification of amyloid peptides in cerebrospinal fluid. Currently, there is no concrete treatment for this disease whereas treatment with dopamine replacement therapy remains in the first line of treatment. However, MAO-B inhibitors are preferred for early management as they provide mild symptomatic benefit with improved signs and symptoms of Parkinson's disease

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