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NANO DRUG DELIVERY SYSTEM IN PARKINSON'S DISEASE: A REVIEW

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder and characterized by progressive degeneration of motor functions due to loss of dopamine-releasing neurons and/or associated neuronal networks and the subsequent depletion of dopamine (DA) levels in the brain area called substantia nigra. There are huge factors that cause degeneration of neurons that leads to symptoms of Parkinson's, such as increase in oxidative stress, overexpression of α-synuclein, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure, and many others. Recent advantages in nanotechnology have provided many options to bypass the various barriers associated with the therapy of CNS disorders and safely deliver drug across the BBB. The present review discussed the problems associated with drug delivery in Parkinson's Disease and provides an information about the recent nanotechnology solutions in Parkinson's. The pros and cons of various novel approaches like biosensors, gene therapy, antioxidants to mention a few have been discussed with the central focus as nano drug delivery system.

KEYWORDS: The present review discussed the problems associated with drug delivery in Parkinson's Disease and provides an information about the recent nanotechnology solutions in Parkinson's.

INTRODUCTION

Parkinson's disease

In the year 1817 James Parkinson, a neurologist described a disease termed Shaking Palsy/Paralysis agitans. Later, around the year 1861 and 1862 Jean-Martin Charcot along with Alfred Vulpian marked a place in medical history for James Parkinson's by addition of more symptoms to his clinical description and coined the umbrella term Parkinson's disease (PD) for those symptoms (Viartisnet[1], 2019). Parkinson's disease is better known as a chronic and progressive neurodegenerative disease (NDs) of the brain and central nervous system (CNS) that occur owing to progressive loss of particular essential neuronal cell (Quek and Hill[2],2017). Men are affected with PD by 1.5 times more than women. Globally, around 10 million people are suffering from PD (Edwards[3] et al., 2016).

Parkinsonism is categorized into two groups: Primary and Secondary Parkinsonism (**Table 1**).

Primary Parkinsonism is also known as idiopathic whereas Secondary Parkinsonism includes drug-induced Parkinsonism, vascular Parkinsonism, normal pressure hydrocephalus, Corticobasal degeneration, Progressive supranuclear palsy, and multiple system atrophy (Parkinson's News Today[4], 2019). PD is also categorized according to symptoms which could be motor and non-motor due to diminished DA level leading to key motor signs and symptoms like bradykinesia and rigidity. Tremor is another characteristic motor symptom where specific areas of the brain like cerebellum, brainstem, and basal ganglia are hugely affected.

Table 1: Classification of Parkinson's Disease.

Type of parkinsonian Disease	Condition
Primary PD	It is an idiopathic PD which is clinical subtypes of PD, such as benign and malignant, tremor, rigid signs or hypokinetic and conditions with/without dementia (Postuma[5]et al., 2015).
Secondary parkinsonism	It consists of several disorders with extrapyramidal symptoms and flourishes as sequentially studied known/ distinguishable etiology factor (Skogar and Nilsson[6] 2018).
Symptomatic parkinsonism + secondary parkinsonism	In this type hypokinesia and rigidity occurs as a result of system degeneration. Tremor is rare in this case in combination with other clinically apparent signs of widespread nervous system involvement. Generally, exist along with clinical symptoms involved in the nervous system (Ugrumov[7] et al., 2011).

Causes, symptoms and pathophysiology

PD occurs in the nigrostriatal bundle, well defined as a dopaminergic pathway connecting pars compacta of substantia nigra along with dorsal striatum ultimately resulting in degeneration of dopaminergic neurons in the midbrain(Singh[8] et al., 2016). NDs like PD comprises of conditions which are sporadic or familial degeneration that affects the ability of the brain's nerve cells to produce neuronal transmitter dopamine (DA) (Modi[9] et al., 2010). In substania nigra these generated DA are released to different parts of the brain and the focal region of release being the putamen and Caudate nucleus. Axons of the DA neurons extend to the putamen and caudate nucleus of the brain and facilitate the release of dopamine (Min[10] et al., 2016). Electrical signals generated from neurons are transmitted with the help of DA and are essential for day to- day physical motion. Therefore, a decrease in DA level for neurotransmission in corpus striatum characterizes PD (Fig:1) and leads to abnormal movements (Surmeieret[11] et al., 2007).

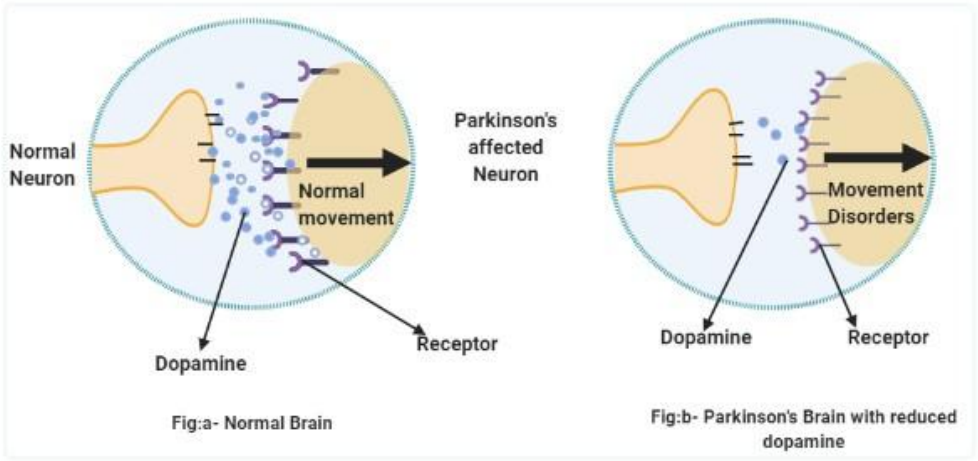

Fig 1: Normal brain and Parkinson's brain.

One of the triggering factors that could lead to PD is malfunctions of the basal ganglia which could lead to movement disorders. Various models have been evaluated and suggested that could explain the pathophysiology motor disorders in PD patients, firing rate and firing pattern model (Nambu[12] et al., 2015). The role of basal ganglia in motor function is well depicted in Fig. 2. The motor features of PD, slow movement as well as resting tremor occurs due to the breakdown in the functioning of two pathways, the direct and indirect pathway resulting in inhibition or slowing down movement (Edwards[3] et al., 2016).

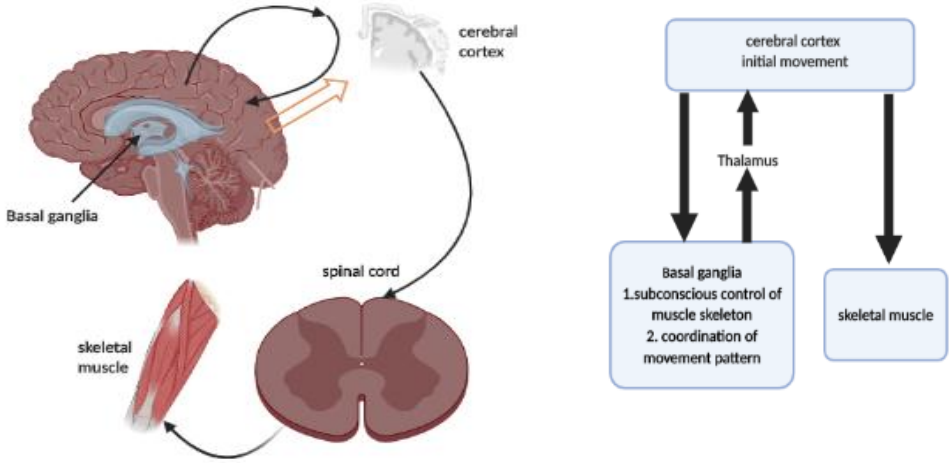

Fig 2: Illustration represents that when the cortex requires to initiate movement it will send signals first to basal ganglia and then the basal ganglia will send the signal back to particularly the motor cortex. Further, the motor cortex receives the signal and initial signals to spinal cord which then is sent to skeletal muscle via ventral horn of spinal cord to generate a smooth controlled movement.

A considerable loss of balance and slowness of motor activities can be observed, during the intermediate stages. In the later debilitating stages, patients typically exhibit severe postural instability, freezing/festination of

gait, walking and functional disabilities (Massano and Bhatia[13], 2012; Mazzoni[14] et al., 2012). Resting tremors include the shaking of body parts (e.g., arms, legs, head) at some rhythmic frequency (3–6 Hz), while bradykinesia characterizes unintentional motor activities and reductions in the intensity or movement. Muscular rigidity, is marked by increased stiffness of muscles. These are the most common signs and reasons attributed to the motor functional instability observed in PD patients (Massano and Bhatia[13], 2012; Mazzoni[14] et al., 2012). Cognitive decline and psychiatric mood fluctuations were also observed in PD progression, which reduces the activity associated with thought processing and increases the frequency of memory lapses (Hou and Lai[15],2007; Watson and Leverenz[16], 2010).

A protein α-synuclein, is the prime hereditary link of PD, whose gene mutation results into the substitution of amino acids alongside occupational exposures such as pesticides, MPTP exposure, herbicides, heavy metals, diet and lifestyle. Head Injury could also be a cause for triggering PD (Singh[8] et al., 2016; Kwakye[17] et al., 2017). In few cases of familial type PD, α-synuclein gene mutation was noticed and accumulation of α-synuclein protein was seen in patient's brain which supports the fact that PD may occur due to abnormal aggregation of these proteins (Henderson[18] et al., 2019).

Current treatments

Current treatment generally used has Levodopa (LD), the drug of choice in the treatment of PD focussing on elevating DA level in brain. The conventional peripheral administration of DA to the brain is encumbered by several biological barriers: it is unable to pass the blood–brain barrier (BBB) due to its hydrophilic nature and displays poor bioavailability with a short plasma half-life (Kwakye[17] et al., 2017; Henderson[18] et al., 2019). Recently, drug delivery systems dependent on nanotechnology are highly encouraging and work upon materials or devices that incorporate nanotechnology are of nanometer-scale (1–100 nm), capable of interacting with biological systems. These technologies interact at the molecular level like blood brain barrier (BBB) cells. The penetrability of nanoparticles (NP) through BBB via in-vitro and in-vivo models are possible. Therefore, in the development of diagnostic tools and nanotechnology-based drug delivery system can be utilized to the fullest. The delivery system can also be engineered in such a way that it can by-pass BBB. More precisely, lipid-based nanodrug delivery systems exhibit positive biocompatibility and can be further functionalized to achieve safe, effectual, and tissue-targeted delivery, particularly to the brain (Saraiva[19] et al., 2016; Karthivashan[20] et al,.2018). This review focuses on lipid-based nanodrug delivery systems in PD.

Drug Therapy for Parkinson's Disease: Limitations and New Approaches

The biggest challenge for effective treatment of PD is the drug delivery to the CNS. In order to solve brain delivery issues, there has been growing interest in the development of nanosystems able to enhance brain delivery of drugs. DDS (drug delivery system) are capable of improving the pharmacological and therapeutic properties of conventional and new drugs, reducing their side effects. Two approaches can be considered for DDS in the management of PD, either direct administration in the brain or systemic delivery for targeted action in the CNS. Depending upon the nature of polymer and material used for its preparation, DDS can be biodegradable or non-biodegradable. Hydrogels and polymeric lipid nanoparticle-based delivery system appears to be the most effective in providing neuroprotection and facilitating the delivery of drugs as well as small molecules to the brain.

In older age groups especially after 40 years, incidences of PD are increasing. Symptoms include bradykinesia, resting tremor and rigidity (Viartisnet[1] et al., 2019). Sleep disorders, neuropsychiatric issues and cognitive dysfunction are also seen in patients with PD. PD mainly affects the basal ganglia. Current treatment focuses on the replacement of dopamine, where precursor of DA, Levodopa (L-DOPA) is given orally. However, detrimental L-DOPA has long term complications that are associated motor complications (Tinazzi[21] et al., 2013). L-DOPA-derived tissues are associated with short-acting dopaminergic agents as suggested by evidences but continuous stimulation may offer better tolerance and some side effects. To extend the duration of the treatment and also release the drug in a continuous manner newer approaches are needed (Garbayo and Ansorenaet[22] et al., 2013). The major challenge in the development of effective PD treatments is crossing the blood–brain barrier (BBB). In order to diffuse from blood into the central nervous system (CNS) molecules must have high lipophilicity, low molecular weight and charge (Brasnjevic[23] et al., 2009). Physiological approach is the most accepted method that increases the transport of therapeutics from blood to brain. The huge capacity of receptor transcytosis is a great advantage. Other strategies include manipulation of the drug, destruction of BBR and finding alternatives routes for the delivery of the drugs (Chen and Liu[24] et al.,2012). We can resolve the issues of brain delivery through micro, nanosystems and thus administration of drugs into the brain tissue (Linazasoro[26], 2008).

Levodopa Delivery System

L-DOPA, a prodrug which is converted into DA in the brain, is the option in PD treatment. However, the major problem is low oral bioavailability of this drug and hence it is combined with carbidopa which reduces the peripheral degradation. The administration of a peripheral AADC inhibitor blocks the conversion to DA outside the brain. This enhances the uptake of L-Dopa inside the brain. The metabolic precursor of Levodopa (L-DOPA) is dopamine. L-DOPA crosses the Blood-Brain Barrier (BBB), where it is converted to dopamine by enzymes such as aromatic amino acid decarboxylase

(dopa-decarboxylase). In the nigrostriatal terminals it is then stored (Garbayo[22] et al., 2013). Nausea, vomiting, cardiac arrhythmias and hypotension are some of the effects seen because most of the drug is decarboxylated to dopamine in the periphery. Thus, requiring large doses of the L-DOPA. As a result of these it is given to the patient with a peripheral dopa-decarboxylase inhibitor (DDI) as Carbidopa, which cannot cross the blood brain barrier (Brasnjevicet[23] al., 2009). There is an increase concentration of LDOPA to Central Nervous System and also a lower dose of LDOPA is needed to be given as DDI prevents the formation of dopamine peripherally (Zhang[27] et al., 2013). To improve L-DOPA therapy, new extended-release formulations are a challenging approach (Cederfjället[28] et al., 2012). In this respect, researchers are focusing on new strategies to deliver drugs more effectively to the CNS (Parkinson's News Today, 2019). LD-DA, which is a prodrug, with longer half-life and lipophilicity increases drug transport across the brain(Park[29] et al, 2014).

Biosensors in Drug delivery

Implanting biosensors in the striatum and other brain nuclei to monitor the levels of dopamine as well as the neurotransmitters (Reichmann[30], 2009). Biosensors are in-vivo drug delivery system capable of determining when a dose is required, then automatically can deliverit. These devices give information regarding the presence and amount of a specific chemical compound in the studied environment. In chemical and physiological condition, combination of a biosensor with a drug delivery system would allow real-time control of drug dosage according to alterations and is expected from ‘‘smart’’ and ‘‘on demand’’ systems (Linazasoro[26], 2008). To combine therapeutic molecules and device technology is the ultimate objective of such devices that resulted to the development of such devices, that are implantable and can provide prophylactic or therapeutic actions. To achieve this goal, the development of new raw materials is need of hour. Considerable interest has been grown in conducting polymers and polymerized ionic liquids such as polycap-Rolactones. One of the major challenges is to achieve balance between small scale of the devices with the quantities of drugs that are clinically necessary. For the treatment of PD, using viral vectors gene transfer in-vivo consist a powerful strategy to overcome the limitation of the BBB. Researchers have found that gene therapy for PD might come up in the reality after facing numerous challenges. To stop or prevent the neurodegenerative course researchers are using the possibility of nanotechnology to condense DNA plasmids into nanoparticles and deliver drugs into the brain.

Gene therapy

Nanomedicine has been explored for the controlled delivery of genes to the brain. The systemic administration of NPs encapsulating DNA encoding for a therapeutic gene has also been investigated. As an example of this approach, Huang and co-workers have recently demonstrated that angiopep-modified NPs encapsulating glial cell line-derived neurotrophic factor (GDNF) gene are able to ameliorate locomotor dysfunction and restore dopaminergic neurons (Huang[31] et al., 2013). In this formulation, angiopep acts as a ligand that specifically binds to a low-density receptor related lipoprotein over expressed in the BBB to facilitate the passage of NPs through this barrier (Huang[31] et al., 2013). Moreover, Hu and co-workers have reported the use of plasmid DNA to decrease or interfere in the expression of α-synuclein (Hu Ket[32] al., 2018). This protein is the major component of Lewy bodies, which are the main anatomo-pathological hallmark of PD. The *in vivo* results demonstrated that NPs were able to recover the neuronal density in the nigrostriatal pathway in a mouse PD model (Hu K[32] et al., 2018). With the same objective, Niu *et al*. developed magnetic Fe3O4 NPs coated with oleic acid molecules (Niu[33] et al., 2017). *N* isopropylacrylamide derivative was photo immobilized onto the oleic acid molecules and short hairpin RNA was absorbed. Following the same method, nerve growth factor (NGF) was also absorbed to *N*-isopropylacrylamide derivative to promote neuronal uptake of particles via NGF receptor-mediated endocytosis. The rationale for using magnetic NPs relies on their small size, large specific surface and superparamagnetic properties. After intraperitoneal administration, the presence of magnetic NPs in the substantia nigra was confirmed by Prussian blue staining (Niu[33] et al., 2017). The intraperitoneal injection of the magnetic NPs was proven to be effective for halting dopaminergic neurons’ degeneration due to the increase of TH expression and the downregulation of α-synuclein. These innovative studies represent an exciting approach to modify the expression of key proteins involved in PD.

Antioxidant delivery

Oxidative stress is one of the most relevant mechanisms involved in PD pathogenesis (Hwang[34] 2013; Blesaet[35] et al., 2015). At the cellular level, the disease is linked to an excessive production of reactive oxygen species, changes in the function of the mitochondrial electron transport chain and accumulation of iron deposition in the substantia nigra pars compacta, among others (Schapira and Jenner[36], 2011; Rodriguez[37] et al., 2014). In recent years for use in PD treatment nanomaterials with antioxidant properties have been developed. Recently, Umarao[38] *et al.* demonstrated the neuroprotective potential in a 6-OHDA rat PD model. He worked on the implantation of superparamagnetic iron oxide NPs directly into the striatum followed by the exposure to magnetic fields and (Umarao[38] et al., 2016). Herein, the atoms of Fe2+ and Fe3+ present on the surface of the iron NPs act as scavengers of free radicals, providing the NPs with antioxidant capacity (Pal[39] et al., 2013). Furthermore, the exposure to an electromagnetic field has boosted the antioxidant effect of NPs via modulating the probability of recombination of pairs of radicals formed. Hence, altering the concentration of free radicals and the level of oxidative stress (Grissom[40] et

al., 1995). It was through the study that greater survival of dopaminergic neurons in the striatum together with a decrease in the percentage of the volume lesioned was observed. An improvement in mitochondrial dysfunction indicates in addition cytochrome c levels were also significantly higher. These findings suggested the development of nanomedicines aimed at decreasing nigral oxidative stress and mitochondrial dysfunction could be a promising strategy for PD treatment through modulation of the oxidative mechanisms involved in dopaminergic neuronal death (Umarao[38] et al. 2016).

Nanoparticles for the systemic administration of drugs

The greatest obstacle for brain drug delivery is BBB. Indeed, 100% of large molecules for the treatment of neurological pathologies and 98% of small molecules cannot cross through the BBB by passive diffusion due to the existence of tight junction gaps. There are thus only a few small molecules that can easily cross the BBB by passive transcellular diffusion, such as some lipid-soluble compounds, some gases, and water (Saraiva[19] et al., 2016). In view of that, NPs may represent systems able to cross the BBB according to their specific characteristics (e.g. size, surface charge and biodistribution). Therapeutic aspects of the pathology itself could also condition the passage of NPs (e.g. drug-cell interactions, dosing and neurotoxicity). This conjunction of factors can act synergistically or separately to prevent the effective passage of NPs through the BBB (Choonaraet[41] et al., 2016). The type of mechanism through which the NPs cross the BBB is dependent on NP characteristics.

Three types of possible mechanisms are expected: simple diffusion, receptor- and adsorption- mediated endocytosis and carrier-mediated transport. Simple diffusion through channels is one of the most limited because of factors such as nanoparticle size, which is not so important when NPs use other mechanisms of passage (Zhou[42] et al., 2018). On the other hand, the covalent binding of specific ligands to the surface of the particles is one of the most interesting strategies to enhance the passage of NPs through the BBB. The passage of NPs is believed due to establishment of specific interactions with the BBB receptors by activating transport systems (e.g., endocytosis, transcytosis) (Tosi[43] et al., 2015). Now a days more focus is on route of administration for NPs through systemic administration.

Importance of nanodrug delivery system in Parkinson's disease

Nanotechnology is a field of research and innovation involving engineering and science dealing with the design, manufacturing, development of materials and devices with particular molecule, atom or compounds. In the area of advanced drug delivery, involvement of nano-based technology has been found to be prominent and important (Soni Yadav[44], 2015). Likewise, with drug delivery via NPs. Researchers have come up with various strategies for drug delivery to brain by successfully crossing the BBB and the limitations of the BBB can be surpassed by these carrier technologies (Tiwari and Amiji[45] 2006). Progression of PD hinge on copious variables in volves assembly of α-Synuclein type of proteins within nerve cells, as well as generation of lewy bodies (toxic proteins), efficient designing of NP can be made to act against α-Synuclein fibrillation or previous formed fibrils through deep understanding regarding the interaction mechanism of α-Synuclein and varied surface attribute containing NPs. In recent years, researches have acquired the understanding that α-Synuclein fibrillation can be prevented by NPs in addition to demolition of fibrils that were preformed through the focussed research in these area (Mohammad-Beigi[46] et al., 2019). Additional advantage of NP drug carrier is lower toxicity due to planned sustained release of the drug. The factors effecting the transport system includes shape and size of NP, class and quality of polymer, type of surfactant and drug molecule (Lockman[47] et al., 2002).

Nanotechnology based dopamine delivery

DA, due to its hydrophilic feature and its high hydrogen bonding potential, does not cross the BBB and its brain administration constitutes a challenge. DA-loaded chitosan NP (DA-Cs- NP) formulation and characterization. An improvement in DA transport across the BBB was observed (Garbayoet[22] al,.2013). In vitro studies confirmed that free-drug is more cytotoxic than DA-Cs-NP. After 3h there was an increase in transport of DA across the cells and oxygen reactive species reduction was observed. Because of its high loading and good delivery capacity for hydrophilic molecules chitosan was chosen (Kulisevsky[48] et al. 2013). Nanoparticles are solid matrixlike colloidal particles comprising of polymers or lipids, administered by the intravenous route and are developed for the targeted delivery of therapeutic agent (Giglio[49] et al., 2011).

Dopamine (DA) agonist

It includes the class of drugs that mimic DA by activating the receptors to generate DA in brain. These drugs bind to DA receptor during inadequate levels of DA (Clarke and Guttman[50], 2002). LD has played a leading role in designing treatment of PD with the help of DA receptor agonists. DA receptor agonists can be classified into two main classes i.e. ergot and non-ergot derivatives. The ergot derivative includes bromocriptine, lisuride, cabergoline and pergolide, and non-ergot derivatives include pramipexole, apomorphine, ropinirole and rotigotine (Antonini[51] et al., 2009). All DA agonists exhibit certain adverse effects like cardiac valvulopathy, somnolence, and repetitious behaviour. Moreover, similar side effects were observed in the case DA and DA agonists excessive somnolence, cardiac valvulopathy and repetitive behaviour (Jain and Waters[52], 2007). The concomitant symptoms of administrating ergots are retroperitoneal fibrosis added to swelling of legs (Alberti[53], 2015).

Ropinirole

Ropinirole following under the class of DA agonist is a non-ergot derivative exhibiting high selectivity toward D2 receptors (Kleweet[54] al., 2008). It is suggested that patients suffering from PD and administrated Ropinirole therapy of marketed product Requip® should be brought to an end over the course of a week. For initiating discontinuation administration is to be brought down to two times daily from thrice daily in 4 days, followed by a reduction in rate of administration to single-dose before absolute withdrawal in last 3 days of the week (Requip-drug[55], 2020). Ataxia, somnolence, fatigue, and hypotension are the associated after effects of other presently administrated DA agonist, although, complications related to motor responses are to a lesser degree (Goldenberg[56], 2008). To overcome the limitations related to conventional ropinirole formulations and increase the uptake of the drug in the brain focus have now been shifted to nanotechnology, especially nano-particle based delivery system.

Rotigotine

Rotigotine, DA agonist used in the treatment of PD. The mode of action of this group of drugs is undetermined but surmised to have the capability to stimulate DA in caudate-putamen, specifically D2 receptor (Le Witt[57] et al., 2007). To facilitate rotigotine delivery for administration over 24 h in a continuous manner a transdermal delivery system, in the form of patch has been designed. This transdermal patch is known as Neupro®. It is advisable before applying the patch that, skin should be intact, clean and dry as well as a 14 days interval should also be maintained before applying the transdermal patch upon previously applied spot (Boroojerdi[58] et al., 2010). The slow drug bioavailability, poor uptake of the drug from the applied surface, interference of arachnoid, choroid plexus and BBB hampers the drug delivery to CNS via dermal route. Hence, many nanocarrier based drug delivery experiments on rotigotine have been carried out by researchers to enhance the delivery of rotigotine to CNS, like intranasal approach with microemulsion-based gel, lactoferrin-modified nanoparticles, microspheres, nano emulsion etc (Choudhury[59] et al., 2017). Choudhury et al. formulated and evaluated rotigotine mucoadhesive nano emulsion for intranasal delivery with an aim to develop an alternative drug delivery approach to solve the limitations associated with its oral delivery system (Choudhury[60] et al., 2019). The formulated rotigotine mucoadhesive nano emulsions (both chitosan-coated and uncoated) were evaluated and results obtained suggests on the basis of nanodroplet size, extended residence time, enhanced penetration across nasal mucosa and stability, when subjected to varied temperature stress and centrifugation. Further, ex-vivo permeation study and in vitro release established that chitosan-coated rotigotine mucoadhesive nano emulsions is superior to uncoated nano emulsion for targeted drug delivery to brain via intranasal administration. Therefore, nano-technology based delivery systems proved to be a encouraging tool for drug delivery to brain.

Advantages and disadvantages of Nano drug delivery systems

Recently, nanotechnology was reported to constitute a substantial revolution in the field of clinical therapeutics by facilitating effectual interactions, stimulation, disease-targeted drug delivery, and theragnostic functions to manage several clinical conditions, including neurodegenerative disorders (Kumar[61] et al., 2017; Chowdhury[59] et al., 2017).

The main objective for nanomedicine is to develop cure for traditionally incurable diseases through the utilization of nanotechnology and also to provide more effective cure with fewer side effects by means of targeted drug delivery systems. Nanotechnology can be directly or indirectly involved in altering the physicochemical properties of drug candidates via masking or loading them into specific delivery systems and increasing their biocompatibility and bioavailability to reach the site of action (Karthivashan[62] et al.,2020)

Diseases can be easily cured with lesser side effects and no surgery is required using nanomedicine in the treatment and are easily detected. The disadvantage in nanomedicine usage is its implementation difficulties and high cost. Nanoparticles coated with proteins allow delivery of drugs to the damaged regions of arteries to fight against cardiovascular disease. (Yadav[63] et al., 2011). The development of nano-technology based sensors capable of sensing various biomarkers at low concentrations in the presence of other analytes and offers affordable diagnostic devices development. Better therapeutic efficacy and enhance bioavailability across BBB for the treatment of CNS disorders can be achieved through nanotechnology-based drug delivery platforms. The different platforms include active targeting using receptor mediated endo- or transcytosis, stimuli responsive nano-carriers and macrophage mediated passive targeting etc. Lastly, nanotechnology can play a role in the developing platforms for effective stem cell therapy through various tissue engineering approaches (Rishi[64] et al., 2015).

CONCLUSION

PD is a multifactorial disorder characterised by loss of dopaminergic neurons, resulting in reduced DA formation, leading to PD associated symptoms and disorders in motor function. PD requires multiple combination therapies to ameliorate symptoms and disease progression in patients. Therefore, treatment of PD is necessary for proper and smooth functioning of body. Presently the conventional drugs available in the market are immediate release, sustained release and OD tablet forms, capsules, inhalers as well as injections which suffers from the major drawbacks of their inability to cross BBB, repetitive dosing, side effects, and incapability to control on-off episodes related to

levodopa (LD). However, the progression of the disease requires a chronic dosage regimen and combination therapies, which further burden patients' lifestyle and impose psychological distress. L-dopa, the gold-standard therapy for advanced PD, has a short half-life, requiring frequent dose increments, eventually inducing dyskinesia and delayed "wearing-off" periods. Over the years various attempts have been made to achieve treatment therapies for PD which will be non-invasive, biodegradable, holds the ability to transport drugs across BBB and deliver at the site of action, keeping account of the side effects. Recently, transdermal patches of DA agonists, such as ropinirole, showed effective sustained release of the drug in plasma; however, patients experienced prominent side effects of the drug, such as sleep disorders and hallucinations. In particular, lipid-based nano drug delivery systems exhibit the lowest toxicity among evaluated biological systems (biocompatible lipids) with enhanced loading/therapeutic efficacy, sustained-release, and safe drug-trafficking properties across the BBB as CNS therapeutics. Therefore, the nanocarrier system seems beneficial in targeted drug delivery as well as capable of providing patient compliance with increase efficacy of drug, reduce side effects and after all provide the likelihood of a normal and healthy lifestyle to PD patients.

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