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NOVELISTIC APPROACHES FOR PARKINSON'S DISEASE MITIGATION: CHALLENGES AND OPPORTUNITIES

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ABSTRACT: In recent times, Parkinson's disease is one of major threat to the population of 1 among 100 in U.S. It is occurring due to dopamine deficiency, which is caused by the degeneration of nigrostriatal dopaminergic neurons. This causes the major clinical motor symptoms of Parkinson's disease. Though the treatment methods are available, the treatment of predominantly non-motor feature are remain a challenge which is caused by the degeneration of non-dopaminergic neurons. The review focused on the challenges and important therapeutic advancements of the disease. This article opens the view on different approaches for dopaminergic, non-dopaminergic drugs for Parkinson's disease and use of novel drug delivery systems such as nanoparticle drug delivery. The motor complications arise from the existing therapy can be controlled by various therapeutic approaches and drug delivery systems. The non motor symptoms of the diseases were poorly recognized and inadequately treated. However, attention is now being focused on the non-motor symptoms, which may be the ray of hope in the treatment of disease in new dimensions. This is the area which arose less concentrated in the previous decades the need for newer and effective agents in the treatment. Still the extensive research has to be focused further. The non pharmacological treatments also may explore in the near future like PD vaccine, Cell transplantation, Gene therapy and surgical methods. The drug delivery system such as TDDS & Nanoparticles drug delivery systems also contribute more for the novel approaches to eradicate the killer disease in coming decades.

KEYWORDS: Nigrostriatal dopaminergic neurons, Neuro-degenerative disorders, Neurotoxins, SLN.

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1.INTRODUCTION

In the world currently many people are affected by neurological disorders such as Alzheimer, Parkinson's disease, cerebral ischemia and brain tumors. The treatment of these diseases is found to be challenging since decades. The main challenge is how to penetrate the BBB (Blood Brain Barrier) for drug delivery [1]. The recent advancements in understanding of these diseases increase the interest in discovering newer molecules in this category which is evident by rapid growth in the pharmaceutical of CNS related candidates. Though many drug candidates are available it is still challenging to cross the blood brain barrier for drug delivery [2]. Various strategies including invasive and non-invasive have been tried to overcome the biggest problem that is a Blood Brain Barrier. Some of the feasible methods which are available include alternating lipophilicity, molecular weight, and charge of active pharmaceutical ingredients. Invasive methods include direct injection, osmotic opening, structural modification and chemical drug delivery methods have tried. This article tries to enlighten various methods excepted for drug delivery to the CNS [3].

CNS barriers

The two main interfaces of brain, which protects neurons from the substances present in the blood including drugs. it also helped in maintaining water homeostasis and proper milieu. these are important for neuronal functions. Those are described as a Blood CSF interface and Blood Brain Barrier.

Blood Brain Barrier

The BBB stand a major challenge for drug delivery to brain so that the treatment of neurodegenerative disorders remains unsolved. the structure of the brain is very specific due to tight junction or zonula occludens mainly composed of interconnected endothelial cells which controls the passage of molecules. For more than 20years various efforts have performed to cross the barrier. The current challenge is to deliver the drug molecule through BBB in a safe and effective manner [1,4].

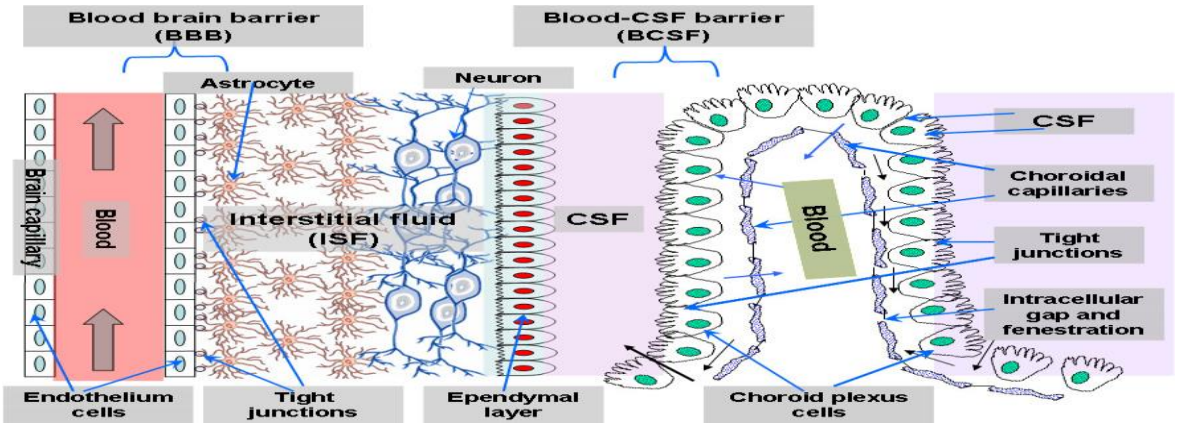

Fig. 1: Schemetic representation of blood brain barrier and blood cerebrospinal fluid [55,56].

Brain Cerebrospinal Fluid

The Blood cerebrospinal fluid (approx. 140ml) acts as a supplement provider for brain and spinal cord. The entire volume is produced and excreted to blood every 4-5 hours for a day. The biological properties of CSF associated with initiation of brain neurogenesis. CSF is secreted by the choroid plexus epithelium which is responsible for neuroendocrine signaling and neuroimmune response [5,6].

The Primary Role of the BBB

BBB completely restricts the free movement of hydrophilic compounds it may be paracellular or may be transcellular. BBB is responsible for the transport of essential nutrients and discharge of metabolites [7]. Lipophilic molecules and gases (Carbon dioxide, Oxygen) communicated through passive diffusion while glucose and amino acids require specific transport [8].

Drug Delivery to Brain

Multiple mechanisms have been approached for the drug targeting to the brain, but a great care must be considered regarding the efficacy, biorecognization, toxicity and KDME of API.

Active targeting: In this method surface modification technique is employed to transport drug with carrier to a specific site. It is of 3 types:

a) First order targeting

b) Second order targeting

c) Third order targeting

First order targeting is restricted towards availability of the system to a targeted organ or tissue. In second order targeting differentiate specific delivery to cell vicinity. Third order targeting includes intracellular localisation to gene or nucleus [5,11]. Further Active targeting differentiated into following:

Ligand mediated targeting: A biologically active molecular ligand (e.g. Anti-body, Polypeptide) helps the drug carrier system to reach their target [9,12].

Physical targeting: The environment changes (e.g. Light, Temperature, pH, Ionic strength, Electric Field) employed to the establishment of drug carrier to pre-identified area.

Dual targeting: The synergistic effect takes the lead where the carrier having its own activity increases the therapeutic efficacy of the drug [10,12].

Double targeting: An ideal combination of temporal and spatial methods to target a carrier system which control the rate of drug delivery as well as specificity.

Passive targeting: The capability of Reticulo Endothelial System (RES) to engulf micro particles

make them an ideal substitute for hepatic targeting.

Invasive targeting: By avoiding the passive uptake of colloids through RES, the normal functioning is suppressed with the help of pseudo colloidal carrier [11,12].

Parkinson's Disease

Parkinson's Disease is a common neurodegenerative disorder in age group of 60-70 years. As per statistics 1 in 500 in the US affected by PD, more prone to male than female (1.8 times). The prevalence will increase in the coming future as per WHO estimated 10 million people worldwide affected by PD which is not an uncommon disease [13].

The major factor for PD initiation is loss of dopaminergic neurons in the substantia nigra, located in the basal ganglia, lower part of the human brain. Clinically evident Parkinson's are due to loss of approx. 82% dopaminergic neuron. Initially developed by trauma in body part with stiffness or slow movement (dyskinesia at a later stage).

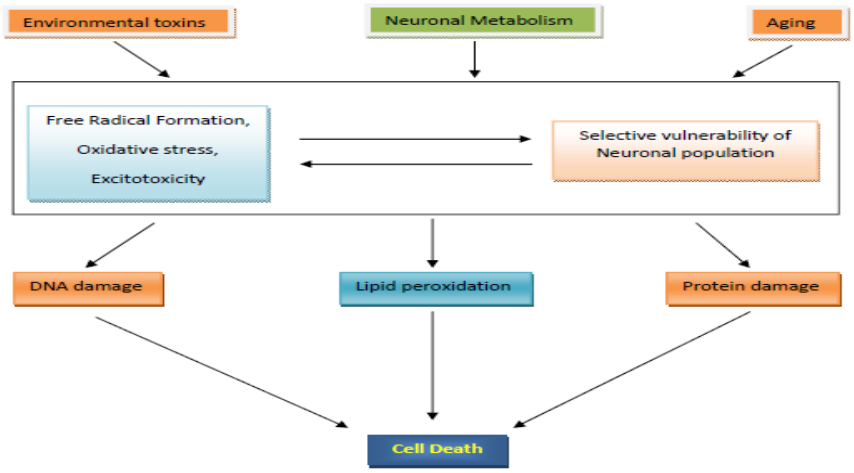

Fig. 2: Schematic Representation of Neuronal Degeneration

The depletion of dopamine in the straitum is the major cause of PD, additionally the presence of Lewy bodies in other cells. There is no current treatment available for the prevention of PD progression [14,15].

Symptoms: The major symptoms are classified into motor and non-motor types.

Motor symptoms.

Bradykinesia: The slowness in the movement or limited range of movement caused by bradykinesia can affect Parkinson's progress.

Rigidity: It causes stiffness and inflexibility of body parts which is uncomfortable and painful (called as Frozen addict).

Tremor: Involuntary shaking, trembling of the muscles of hand and foot. It occurs in resting state of the person.

Postural instability: At late stage of PD, the complaint of dizziness is common that is incapable of maintaining an upright posture. This is also called retropulsion.

Non-motor symptoms.

The non-motor features apart from movement disorders, have a major impact on the quality of life. Early recognition and treatment is useful to overcome this problem [16,17].

Causes

The exact causes of Parkinson's is still a mystery, but the multiple contribution of various factor leads to PD development, which may be genetic or environmental or both.

Genetic: Eleven genes have been traced by genetic linkage and six genes identified as a probable causative agent for the commencement of PD, i.e. α-synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), Parkin (PRKN), LRRK 2, PINK 1 and DJ-1 genes. Among 6 genes LRRK 2 gene (PARK8) is the most common cause for PD having the frequency approx. 7%. The initiation of PD is associated with the degeneration of Dopaminergic neurons of substantia nigra. With the continuous downfall the severity is directly proportional to dopamine deficiency and may be corrected by immediate replacement with L-dopa. Studies reveal that a gene encoding α-synuclein (a lipid binding protein) identified as the basis for inheritance of PD. It is a major component of Lewy bodies. Families with genomic triplication of α-synuclein gene are more susceptible. The study reveals the direct relationship between Parkin gene and PD. The difference between Parkin linked PD and α-synuclein linked PD is the absence of Lewy body. A third gene responsible for PD deubiquitination enzyme UCH-L1 a mutant protein [13,18,19].

Environmental factors: The toxic chemicals like MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine) is a causative agent for initiation and development of PD. The exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which is a neurotoxin capable of inducing Parkinsonian in humans. This factor has been confirmed by various epidemiology studies which reveals that the rural residence, well-water drinking and exposure to herbicides and pesticides play role in development of PD. The possible etiology of PD was traced to the compound MPTP that is a contaminant to heroin substitute. It causes irreversible destruction of dopaminergic neurons. MPTP converts to a toxic metabolite $MPP^+$by the enzyme monoamine oxidase (MAO). MPP^+ selectively acts on dopaminergic neurons and inhibits mitochondrial oxidation reactions. Other herbicides such as rotenone also has proved to be a causative agent for PD [19,20].

Diagnosis

Unfortunately, there is no standard diagnostic testing for PD. The diagnosis of Parkinson's is first made by an internist or family physician. Many people seek an additional opinion from a neurologist with experience and specific training in the assessment and treatment of Parkinson's disease referred to as a movement disorder specialist. To diagnose Parkinson's, the physician takes a careful neurological history and performs an examination. Diagnosis of Parkinsonian syndrome includes: Movement disorders, Muscular rigidity, Postural instability, and Tremor [21,22].

Recent developments in Parkinsonian management

Currently, two new therapies found for the patients suffering from chronic progressive neurological disease, i.e. PD, they are vaccines and monoclonal antibodies (MAb). A parenteral MAb leads to a direct treatment, whereas the vaccines strengthen the immune system. Collectively, they are called as immunotherapy for PD. The first MAb i.e. PRX002 for PD is under trial. The recent research has reviled the connection between the intestinal microbiota (microbes) with CNS, feasible causative agent for PD pathology [23,24]. Dopamine agonist monitoring strategy: The Dopamine agonist drugs strongly associated with impulse control disorder. as per the FD report 2.7 million serious cases were reported between 2003 to 2012. These were due to dopamine receptor agonist and dopamine receptor drugs. So strict monitoring is required before prescribing the above drugs [25,26].

Treatments available

Modern advancement for the treatment of PD includes neurological treatment (neurografting) specific rehabilitation, specialist nursing, tributaries towards Parkinson's patient. The major drawback for the treatment of PD based upon systemic uptake of API and redistribution across the BBB and into CNS. A multidisciplinary approach has to be considered for multi-factoral syndromes of Parkinson's (Table 1).The major ambition of Parkinsonism therapy is to increase the dopamine level, stimulating the arena of dopamine in the CNS, block the effects of Acetylcholine or other enzymes which reduce the effectiveness [13,14].Alternative therapies can be considered for direct intervention with CNS. These include neurosurgical approaches which bypass the BBB. It requires implantations of IPG (implantable pulse generator similar to a pacemaker producing electrical signals to brain for the stoppage of dyskinesia) [17,18,21,22].

Advanced invasive techniques for Parkinsonism

Recently, some physical based techniques approached for mechanical breaching of BBB. They are:

- Intra-cerebro-ventricular (ICV) infusion
- Convection-enhanced delivery (CED)

- Microchip system or Implants
- Disruption of BBB

All the above methods have employed for direct delivery of therapeutics in the CNS.

ICV infusion

The therapeutics concentrate at a very low percentage of 1-2% in CSF in Brain. By general circulation the therapeutics can distribute itself to BBB arena, so it can be predicted a slow i.v. infusion can help to transport the drug to cross the BBB. But the pharmacological effect will be synergies in combination with target receptor, meanwhile the conditions must be maintained and the target receptor must deliver the therapeutic in close vicinity [27].

CED

Convection-enhanced delivery is an innovative idea of bypassing BBB by direct infusion into the CNS. CED can be implemented by the help of a micro catherater insertion into brain parenchyma for 2 hours for continuous infusion. With a limitation for right identification of location in brain [28,29].

Implants

The successful implantations of intra-cerebral neurotrophins device can be helpful for the local release in the brain. Biodegradable polymeric implant can be helpful in this approach. The limiting capacity of this technique is related with implantation distance from desire [30,31].

Table 1: Drugs available for the treatment of Parkinson's Disease.

a) Carbidopa/Levodopa Therapy

Medication	Formulation	Available doses	Side effects	Interactions	Indication	Special comments	Marketed brand
Carbidopa/ Levodopa	1)Tablets 2)Tablets controlled release	1) 10/100, 25/100 mg 2) 25/100, 50/200 mg.	Euphoria, Low blood pressure, nausea, confusion, dyskinesia, dry mouth, dizziness	Antacids, anti-seizure drugs, anti-hypertensives (Phenytoin),anti-depressants (isocarboxazid , phenelzine)	First course of treatment.	Should not be given to women who are breast-feeding	Sinemet, Sinemet CR, Parcopa

b) Dopamine agonists

Medication	Formulation	Available doses	Side effects	Interactions	Indication	Special comments	Marketed brand
Apomorphine hydrochloride	Subcutaneous injection	.02mL– .06Ml three times a day	Voluntary Movement Difficulty, Low blood pressure, nausea, chest pain, Excessive Sweating,dizziness	5HT-3 Antagonists, Cisapride, Droperidol, Sparfloxacin, Citalopram	Adjunct levodopa therapy to treat “off” periods	Increased possibility of systemic side effects when given to people over age of 60	APOKYN
Bromocriptine	Orally	2.5 mg 5 mg	Nausea, constipation, dizziness,drowsiness, loss of appetite, vomiting,	Antihypertensive drugs(methyldopa) ,betablockers (metoprolol),	First course of treatment alone or with levodopa	Can cause a dangerous increase in blood pressure during	PARLODEL

			diarrhea	antipsychotic medication.		pregnancy	
Ropinirole	Tablets, Extended release tablets	.25mg-5mg	Constipation, dizziness, drowsiness, weakness, unusual sweating, headache, and dry mouth	Antipsychotics (chlorpromazine), (cimetidine, fluvoxamine, mexiletine, omeprazole), estrogens, metoclopramide	Used alone or with other medications to treat Parkinson's disease	Higher incidence (10%) of hallucinations in the elderly.	REQUIP
Rotigotine	Transdermal patches extended release	Initial: 2 mg patch, Advanced-stage Parkinson's disease: 4 mg patch	Burning, itching, redness, skin rash, swelling, or soreness at the application site. Swelling of the hands, ankles, feet, or lower legs	Using rotigotine together with ethanol can increase nervous system side effects	Used for the treatment of moderate to severe parkinson's disease	Rotigotine may cause sudden onset of severe drowsiness or may even fall asleep during normal daily activities (eating, talking, driving).	NEUPRO

c) Anti-cholinergics

Medication	Formulation	Available doses	Side effects	Interactions	Indication	Special comments	Marketed brand
Benzotropine mesylate	Injection	.5 mg	Drowsiness, dizziness, constipation, flushing, nausea, nervousness, blurred vision, or dry mouth	Anticholinergics/antispasmodics, amantadine, corticosteroids, MAO inhibitors	Secondary medication; tremor; attempts to restore balance by inhibiting other enzymes and nerve cells that may attack dopamine	Should be used only when clearly needed during pregnancy	COGENTIN

d) MAO-B inhibitors

Medication	Formulation	Available doses	Side effects	Interactions	Indication	Special comments	Marketed brand
Selegiline	Tablets	5 mg	Abdominal pain, dry mouth, nausea, stomach upset, trouble sleeping, and headache	Antidepressants, other MAO inhibitors, appetite suppressants (such as diethylpropion), drugs for attention deficit disorder	Tertiary medication; controls brain's metabolism of dopamine	Avoided in adrenal gland tumor, cerebrovascular disease (e.g., stroke),heart problems	Eldepryl, Carbex

e) COMT inhibitors

Medication	Formulation	Available doses	Side effects	Interactions	Indication	Special comments	Marketed brand
Entacapone	Orally	200 mg	Vomiting, diarrhea, unwanted/uncontrolled movements, increased sweating, drowsiness, tiredness, dry mouth, gas, and abdominal pain	Certain MAO inhibitors (isocarboxazid, linezolid, methylene blue, moclobemide, phenelzine ,procarbazine, tranylcypromine).	Used with other medications (levodopa/carbidopa) to treat Parkinson's disease	During pregnancy, this medication should be used only when clearly needed.	Comtan
Tolcapone	Orally	100 mg 200 mg	Diarrhea, headache, drowsiness, trouble sleeping, increased number of dreams, increased sweating, dry mouth, gas, and abdominal pain.	Certain MAO inhibitors(isocarboxazid, linezolid, methylene blue,moclobemide, phenelzine,procarbazine, tranylcypromine).	Tertiary medication for motor fluctuations; limited in use to those who have exhausted other treatment	This drug may make patient dizzy or drowsy	Tasmar

Disruption of BBB (BBBD)

BBBD has reported the most effective way for direct delivery of therapeutics inside the brain, but it is not free from undesirable effects. The disruption of the BBB has an advantage to open the tight junction between endothelial cells and brain capillary [32]. Various approaches for BBBD are osmotic disruption, ultra sound disruption, application of bradykinenin. All the above approaches leads to patient non-compliance, high cost of therapy, hospitalization requirement and chances of permanent damage of neurons [33].

Non-invasive approaches and other routes for CNS drug delivery

Pro-drug approach

Pro-drug based CNS targeting has improved its characteristics, after undergoing the chemical conversion. The metabolites produced acts as main active pharmacological agent. This prodrug approach is a good idea to alternate or improve physicochemical properties. The Mechanism of action of pro-drug relies on closure and longer contact with the receptor. Example, the accessibility of morphine through CNS only can be affected after acetylation of both hydroxyl group i.e. prodrug of morphine. Still pro-drug having some limitation that is alternation of original tissue and of efficacy and toxicity of the parent drug. Sometimes it may cause increased tissue burden [34,35].

Redox chemical delivery

It is a novelistic approach of targeting to a specific target organ by chemical reaction and enzyme activation. The lies of bond lead to release of the API, it contains two moieties, one targeted moiety responsible for site specificity where as the other is modifiable, serve as a protector [36,37].

Pulmonary/Nasal delivery

This technique involves the delivery of drug through the respiratory tract so that it can reach to the deepest layer, but having a constant of particular size and density. The drug particles must have a nano scale range and a density of less than $0.4 g/cm^3$. The choice of the drug of nasal route are phospholipids, amino acids or their combinations. The required dose is 33% of an oral dose [38,39].

Receptor mediated delivery

This strategy is based upon the bonding between non-transferable protein/peptide to a transferable protein/peptide with the help of transcytosis where a receptor or vector takes a lead role to cross the BBB. A vector may be a modified protein or receptor specific monoclonal anti-bodies. The above technique is based on chimeric peptide technology. Another approach is the attachment of the drug with transporting an vector by an amide linkage so that the cleavability will minimise [40].

Other approaches for drug delivery to Brain

Multiple attempts have tried with carrier mediated drug delivery to the CNS, they are briefly discussed to know their agility in drug delivery to desired areas.

Liposomes

Liposomes are lipid bilayer vesicles first designed by Bangham. These are the vascular structure

consisting of an aqueous core covered with a hydrophobic lipid bilayer. The lipid employed are phospholipids so that compatibility with biological components and minimising adverse effects. Liposomes act as an ideal carrier for drugs, biotechnologicals, anti-cancer molecule as well as micromolecules. The anti-cancer chemotherapy through liposomes reduce systemic toxicity. The advantages with liposome is to incorporate both hydrophobic and hydrophilic molecules through a single delivery having multiple options in size from 15nm to several mm. The wide range in size and unique characteristics (both hydrophobicity and hydrophilicity) makes it more utilisable. As per the recent study a nanosize liposomes (nanoliposomes) show a selective tumor localisation [41,42].

Nanoconjugates

As the name suggests nanoconjugates consists of covalently attached three functional domains, i.e. targeting group, a linker and a drug. It gives tissue specificity and maximum efficacy. The major concept behind is nanoconjugates are multi-targeting [43,44].

Nanoparticles

Nanoparticles are solid colloid particles ranging from 1 to 1000nm in size. Nanoparticles found to be helpful because the active drug is either dissolved or entrapped or encapsulated. Nanoparticles of different size, shape, material, physicochemical properties can be designed. The various classes of nanoparticles are:

Mutli-functional:- They are coiled as Nanomedicine. e.g. Solid lipid nanoparticles(SLN), polymeric nanoparticles and many more. SLN consists of a solid lipid having a size range of 50-1000nm in colloid drug delivery. Polymeric nanoparticles composed of a core material matrix with an embedded drug having a size range of 60-200nm[45,46].

d) Nanoshells

Nanoshells consist of a special class of nano composite material which are highly functional. Particularly nanoshells contain a dielectric material coated a thin layer of another material with the help of specialised technique. The term nanoshell is used because of the thickness of the cell, i.e. 1-20nm. They are highly stable, chemically inert and water soluble in nature. Nanoshells offer advantages over conventional drug delivery and helpful in biomedical imaging and therapeutic applications[47].

e) Quantum dots (QD)

Particles smaller than 5nm are quickly cleared by renal filtration, this technique is used in designing of Quantum dots. QD are semi-conductor nanocrystals having the size range of 2-10nm and after encapsulation increases to 5-20nm. QD acts as a imaging contrast agent. This nanostructure behaves like a magic bullet which identify to the specific organ or tissue and treat it. The neurodegenerative disorders can be successfully treated by the help of QD. They are light sensitive, semi-conductive particles with few nm sizes [48].

f) Superparamagnetic nanoparticles (SPIONs)

These nanoparticles contains an iron oxide core coated with an organic or inorganic material having the size range of 5-100nm. The edge of these nanoparticles over other types is magnetic resonance imaging (MRI) visualization. The coating material may be either inorganic (silica or gold) and organic (phospholipids, polysaccharide and polymers). The biological activity of these types of nanoparticle is based upon magnetisation theory which trigger the action by external magnetic field. The potential application of SPIONs is under research, already marketed products of SPIONs are available for diagnostic purpose [49-51].

g) Fullerenes/Nano"onions"

The major component (99.9%) of fullerense is carbon, which sometimes referred as carbon nanotubes or buckyballs, they may be a single or multi layer. The multiple layer called as nano"onion", spherical in size with multilayered core, these mutlilayer are dedicated to lubricants. The fullerenes composed of approx. 300 carbon atoms and it holds a great promise in health care applications. Research reveals that the therapeutic anti-oxidant property of fullerenes provides a great support towards the treatment of CNS degenerative diseases. Fullerenes can capture multiple electrons derived from oxygen free radicals in unoccupied orbitals. These have potential applications in the treatment of disease where oxidative stress plays a role in the pathogenesis, such as degenerative diseases of the central nervous system including Parkinson’s disease[52].

h) Dendrimers

Dendrimers are multi-branched and mono-dispersed 3D molecules with a specific molecular weight (MW) having a size of approximately 20nm. Dendrimers first discovered in 1978 by Fritz Vogtle and coworkers. Dendrimers appears just like an architectural tree branching from a central point. Dendrimers are meant for parenteral delivery directly to the tumor tissue. The mechanism of action of dendrimers is based on two models:

1) Passive targeting via enhanced permeability retention (EPR)

2) Active targeting by receptor mediated cell specific targeting [53,54].

2. CONCLUSION

The treatment of Parkinson's disease is particularly challenging because the delivery of active molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the Blood Brain Barrier (BBB), Blood Cerebrospinal fluid Barrier (BCB) and Blood-Tumor Barrier (BTB). The present outlook for patients suffering from many types of brain diseases remain poor, but recent developments in drug delivery techniques provides reasonable hope that the formidable barriers shielding the brain may ultimately be overcome. Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery system. Substantial progress will only come about, however, if continued vigorous research efforts to develop more therapeutic and less

toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to brain targets.

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CONFLICT OF INTEREST

The authors hereby declare no conflict of Interest.

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