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Improvement in Drug Delivery System for Parkinson's Disease

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***Abstract*—This paper is about the most promising and upcoming agents in the field of PD drug discovery and discussing improvements made in the brain drug delivery system for Parkinson's disease. Numerous promising perspectives are provided in this paper by rasagiline, dopamine and levodopa delivery and the disease modifying strategy that slow or stops the progression of the disease.Few neurological diseases have received much attention and investment in research as Parkinson's disease.**

Keywords—PD-Parkinson's Disease, BBB-Blood Brain Barrier, CNS-Central Nervous System, DA-Dopamine.

I. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder. The characteristic is the damage of the nigrostriatal dopaminergic systems that causes the loss of dopamine inside the brain[1]. In, Parkinson's disease**,** the pigmented neurons of the substantial nigra, locus caeruleus, and other brain stem dopaminergic cell groups are lost. The cause of the disease is not known[2]. The loss of substantial nigra neurons, which in the caudate nucleus and putamen, results in a decrease of the neurotransmitter dopamine[3]. Onset is generally after age 40, with increasing incidence in older age groups. Symptoms are bradykinesia, resting tremor and rigidity[4]. PD patients also suffer from sleep disorders, neuropsychiatric issues and cognitive dysfunction. PD affects the basal ganglia[5]. The current treatment is based 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[6]. There is evidence that l -DOPA-derived issues are associated with short-acting dopaminergic agents. A continuous stimulation may cause better tolerance and some side effects. Thus, new approaches are needed to extend the duration of the treatment and also release the drug in a continuous manner[7].The major challenge is crossing the blood–brain barrier (BBB) in the development of effective PD treatments. Molecules with high lipophilicity, low molecular weight and charge are able to diffuse from blood into the central nervous system (CNS)[8]. The most accepted method is physiological approach that increases the transport of therapeutics from blood to brain. The advantage is the capacity of the receptor transcytosis. Other strategies includes manipulation of the drug, destruction of BBR and finding alternatives routes for the delivery of the drugs[9]. We can solve the issues of brain delivery that is done by micro and naosystems and thus administration of drugs into the brain tissue."[10].

II. Research Method

After reading few of the journals' I came up with some of the research methods that were used to improve the drug delivery for the improvement of Parkinson's disease. In the research method section I would like to share few of the recently used research techniques that are used for treating Parkinson's disease.

The pharmacologic and therapeutic properties of conventional and new drugs are improved by the DDS and also the side effects are reduced. For Parkinson's disease, DDS includes local treatment where the drugs are directly administered into the brain or systemically administered for a targeted action in the CNS[3]. Dopamine does not cross the BBB (blood brain barrier) because of its high hydrophilicity and its high potential for hydrogen bonding. A study was done with nanoparticles that are composed of chitosan. Chitosan has high loading and better drug delivery capacity for hydrophilic molecules. The purpose of this study is to find the potential of chitosan for the delivery neurotransmitter Dopamine (DA) into the brain. CS based NPs were incubated with DA at two different concentrations and they were labeled as DA/CSNPs (1) and DA/CSNPs (5), accordingly. The absorption of DA onto NPs DA was checked by X-ray Photoelectron Spectroscopy (XPS) analysis[11]. Transport studies across MDCKII-MDR1 cell line showed that DA/CSNPs (5) give rise to a significant transport increasing effect compared with the control and greater than the corresponding DA/CSNPs (1)[12]. Measurement of reactive oxygen species (ROS) gives a low DA/CSNPs neurotoxicity after 3 h. *In vivo* brain microdialysis experiments in rat showed that intraperitoneal acute administration of DA/CSNPs (5) (6–12 mg/kg) induced an increase that is dose-dependent in striatal DA output. Thus,

these CS nanoparticles represent an interesting technological field for DA brain delivery and, hence, may be useful for Parkinson's disease treatment. " [13]p.102".

DRUG DEVELOPMENT SYSTEM FOR PARKINSON'S DISEASE

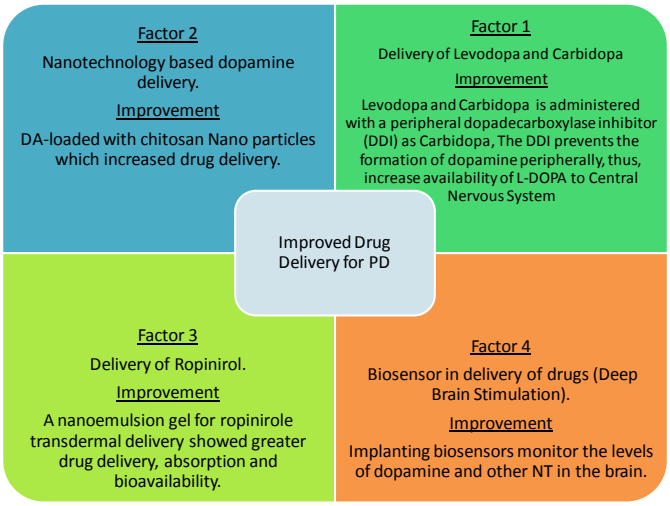

Figure 1: Improved Drug Delivery System for Parkinson's disease.

Factor 1 (Drug development system for l-DOPA delivery)

"The administration of a peripheral AADC inhibitor blocks the conversion to DA outside the brain. This increases the uptake of L-Dopa inside the brain. [14]P.3".The metabolic precursor of Levodopa (L-DOPA) is the dopamine. The 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[7].In the periphery most of the drug is decarboxylated to dopamine, resulting in effects such as nausea, vomiting, cardiac arrhythmias and hypotension. 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[8]. There is an increase concentration of L-DOPA to Central Nervous System and also a lower dose of L-DOPA is needed to be given as DDI prevents the formation of dopamine peripherally[15].

To improve l-DOPA therapy, new extended-release formulations are a challenging approach[14]. In this respect, researchers are focusing on new strategies to deliver drugs more effectively to the CNS[15].LD-DA, which is a prodrug, with longer half-life and lipophilicity increases drug transport across the brain[16].

Factor 2 (Nanotechnology based Dopamine Delivery)

"DA-loaded chitosan NP (DA-Cs- NP) formulation and characterization. An improvement in DA transport across the BBB was observed.[7]p.4". In vitro studies confirmed that free-drug is more cytotoxic than DA-Cs-NP. After 3 hr 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[5]. These nanoparticles are solid matrix-like colloidal particles which are composed of polymers or lipids and are mostly given by the intravenous route and are developed for the targeted delivery of therapeutic agent[17].

Factor 3 (Ropinirole transdermal delivery as nanoemulsion gel).

"A nanoemulsion gel for ropinirole transdermal delivery showed greater drug delivery, absorption and bioavailability.[18]p.1".A ropinirole transdermal delivery which is a nanoemulsion gel, showed improved drug delivery, drug absorption and improved bioavailability compared to the conventional oral tablets and conventional gels.A significant results compared to oral administration of the drug as tablets was found where the biochemistry parameters were significantly reversed and increased after administration of the drug as transdermal nanoemulsion gel[19]. A substance can be continuously delivered through the skin and thus continuous dopamine replacement therapy by a patch is possible. In order to avoid dyskinesia and other motor complications a continuous stimulation of the dopamine receptor is needed. Such as a silicone-based transdermal patch is used to deliver Rotigotine. Because of its lipophilic property, hydrophilic property, the routes of skin penetration are transcellular and intercellular. It has been shown that a constant delivery which is independent of the type of the skin and the part of the body to which the patch is applied, is obtained by the rotigotine patch.

Factor 4 (Biosensors in Drug delivery)

" Implanting biosensors in the striatum and other brain nuclei to monitor the levels of dopamine and other neurotransmitters. [18]p.4".Biosensors are in vivo drug delivery system which is able to determine when a dose is needed and then can deliver it automatically. They are the devices that give information regarding the presence and amount of a specific chemical compound in the studied environment. The response is related to a property that is directly proportional to it. The ''smart'' and ''on demand'' systems, would allow real-time control of drug dosage in chemical and physiological status according to alterations and they are a combination of a biosensor with a drug delivery system[10] . Its ultimate objective of such devices is to combine systems that can combine therapeutic molecules and device technology. This result in the formation of devices that are implantable and can give prophylactic or therapeutic actions. For this purpose, the development of new materials is needed. Conducting polymers and polymerized ionic liquids such as polycap-Rolactones are of considerable interest. The small scale of the devices with the quantities of drugs that are clinically necessary is needed to be balanced which is one of the major challenges. 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 came up in the reality after facing numerous challenge. To stop or prevent the neurodegenerative process researchers are using the feasibility of nanotechnology to condense DNA plasmids into nanoparticles and deliver drugs into the brain.

III. Discussion of Model:

Drug development in PD is mainly focused on: (i) Drugs that are reformulated (ii) development of small molecules and gene and cell-based approaches. The objective of drug development for PD is to control the motor symptom.The brain is protected from unwanted, harmful substances and invading organisms by the blood–brain barrier (BBB) which is a dynamic barrier. It is also prevents transportation of drugs into the brain.In PD most of the drugs are given by orally. The path from the mouth to the dopamine receptor is a very large distance. Factors such as, stomach pH and rate of emptying, dietary proteins, constipation are considered which determine the availability of antiparkinson's drugs in the blood (especially Levodopa) and thus the motor response. Other routes of administration such as intranasal, rectal, sublingual or pulmonary and none of them has shown to provide continuous stimulation of dopamine receptor .Thus other routes of drug delivery systems, such as infusion pumps and skin patches, are now being used in PD. The subcutaneous delivery of apomorphine and intraduodenal delivery of Levodopa are done by infusion pumps. Their main objective is to provide a more continuous and physiological stimulation of dopamine receptors[2]. A maintenance of drug levels continuously in therapeutically desirable dose, due to targeted delivery to a particular cell type tissue there is a reduction of harmful side effects, decreased amount of drug needed, decreased number of dosages leading to improved patient compliance, for pharmaceuticals with short half-lives there is a facilitation of drug administration , are obtained by improved drug delivery system .To support and provide damaged neurons regeneration, to give neuroprotection and to enhance the delivery of drugs and small molecules across the blood-brain barrier. All of them are can improve current treatment of Parkinson's disease (PD). " [10]p.1''.At two different region in the brain, patient with Parkinson's disease respond to deep brain stimulation (DBS) .To send a finely tuned electrical current in order to stimulate the brain an implantable battery is needed. A pacemaker-like device is implanted in the brain. When patients is given DBS for Parkinson's, a very fine wire into one of two deep brain regions, the subthalamic nucleus (STN) or the globuspallidusinterna (GPi) are involved in motor control. Often, when the wire is placed properly and the stimulator turned on, a improvement of motor symptoms can be found[20]. It is considered most effective by stimulating on both sides of the brain, or bilaterally.

IV. Importance of Model:

As described above drug delivery inside the brain is a challenge for the researchers. Only small molecules with high lipophilicity can easily cross the BBB.To overcome this problem many approaches have been taken such as reformulating the existing drug, developing small molecules,hydrogels and polymeric or lipid micro particles and nanoparticles are the most effective in protection of the neurons and facilitates the delivery of drugs and small molecules inside the brain[6]. There are various ways by which drug delivery inside the brain can be achieved. Such as the transdermal patch where the drug as nanoemulsion gel is delivered continuously, avoiding fast-pass metabolism, and applied once daily. On the other hand this has got some limitations too. Such as allergic reaction at the application site may occur, lower concentration of drugs per square centimeter, patch may be difficult to take off and apply. To provide prophylactic or therapeutic actions miniaturized devices for drug delivery such as micro to nanoscale system can be used that combine device technology with therapeutic molecules to allow the development of implantable devices[21]. The small scale of the devices needed to be balanced with the amount of drugs that is needed is one of the major challenges. These are based on biosensors, devices that can give information regarding the presence and amount of a specific chemical compound in the studied environment[22]. Nanoparticles are solid matrix-like colloidal particles made of polymers or lipids and are given by the intravenous route and they are developed for the targeted delivery of drugs or imaging agents. They can be useful in drug delivery inside the brain, such as the sustained release of peptides, proteins, genes or antisense drug. Biosensors also monitor neurotransmitter levels in targeted regions in the brain (dopamine). The nano-enabled drug delivery systems developed for the treatment of PDs, nanotechnology may contribute significantly taking the advantage of the nanoscale structures of cells in the brain that is the neural cells. For the of CNS disorders treatment, targeting the material, device, or drug to the site always with the therapeutic approaches remains challenging. The nature of this area of research is highly interdisciplinary , it is also important that in conjunction with basic and clinical neuroscience advancements, technological advancements is needed[23]. According to my point of view nanomedicine, the use of nanotechnology to healthcare provides a great challenge for medical treatments, faster diagnosis and drug delivery to the brain.

V. Conclusion

In the past decade, there is always an attention and effort given for the development of modern and novel drug delivery systems to cross the BBB. Industry, government and academics are seeking effective drug therapies for the increasing incidence of brain disease associated with a huge number of populations face the challenge for PD treatment.Targeted delivery systems into the brain must be targeted for their safety, risk and benefit for patients. The treatment of PD represents a major challenge. In the later stages of PD, bradykinesia is treated by Levodopa and/or similar dopaminergic preparations effectively, without causing severe drug-related involuntary movements. Finally, the challenge of developing an effective neuroprotective therapy for PD is needed. In some specific targeted drug delivery systems nanoparticles have shown a great improvement in patient. So there is a wide scope to develop medicines as nanoparticles, which will specifically target the CNS. In the new drugs development for the central nervous system the blood-brain barrier (BBB) is one of the main challenging factor. A further improvement in nanoparticle based drug delivery technology should be done, so that it can be safe, effective, target oriented and also cost effective.

VI. ACKNOWLEDGMENT

Christian Bach serves as an assistant professor of Technology Management and Biomedical Engineering. He holds academic honor as: PHD in information science and executive MBA at Albany/SUNY.

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