Advances in Nanotechnology for Targeted Drug Delivery in Central Nervous System

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Abstract:

Patients who are suffering from illnesses that influence the central nervous system (CNS) struggle with getting medicine because of the presence of two barriers: the blood-cerebrospinal fluid boundary and the intrinsic blood-cerebrum obastruction (BBB). Both of these barriers make it hard to safely give prescription. There are various neurological conditions that are routinely perceived, including Alzheimer's disease, frontotemporal dementia, amyotrophic parallel sclerosis, Parkinson's disease, and Huntington's disease, to give some examples. In addition to these disorders, there are some that can affect the neurological system. Nanotechnology in drug conveyance systems is one therapy strategy that has the possibility to be powerful in the treatment of specific ailments. This is because nanotechnology has the capacity to control the distribution of drugs. To conquer the problems that have been presented and making progress in the conveyance of medications to the central nervous system, various approaches have been created to be successful. This research was completed determined to cast light on late advancements in the field of nanotherapeutics research and the possible consequences of these advancements in the treatment of illnesses that disable the central nervous system. The research was completed with the target of shedding light on these advancements. Another subject that is investigated is the challenges that are experienced while endeavoring to bring nanomedicine from the research facility to the bedside with the end goal of clinical application.

Keywords: Nanotechnology, Advancement, Central Nervous System (CNS), Drug Delivery

I. INTRODUCTION:

The blood-brain barrier (BBB), which is a barrier that hinders the conveyance of therapeutic drugs, is a significant barrier in the treatment of disorders that influence the central nervous system (CNS). Methods of medication conveyance that are based on nanoparticles have demonstrated that they can possibly beat these challenges and work

on the adequacy of treatments for illnesses of the central nervous system. There are various advantages that accompany these systems, including the capacity to encapsulate a large number of therapeutic compounds, broadened flow durations, and increased drug stability [1].

The capacity of nanoparticles to target specific parts of the brain, work on their stability, and result in superior medication release patterns can be generally worked on through the process of nanoparticle change. They are fit for encapsulating a wide assortment of therapeutic substances, including proteins, nucleic acids, minuscule chemicals, and tools for altering genes, among hundreds of other examples. It is also possible for them to use various ways of medication conveyance, co-conveyance efflux siphon inhibitors, or modification of medication release kinetics to dodge multidrug resistance mechanisms in disorders of the central nervous system.

There are two components that make up the central nervous system: the brain and the spinal string. This is because the brain is responsible for our thought process, learn, move, and feel. Between the brain and the nerves that are distributed all through the body, the spinal line is responsible for transmitting messages in the two directions.

The brain is covered by the bones of the skull, and the spinal string is safeguarded by vertebrae, which are a gathering of ring-shaped bones [2]. Both the brain and the spinal rope are safeguarded by bone for their respective functions. Cerebrospinal fluid and layers of membranes known as meninges make up the cushioning that each of these structures have. The fluid travels via the ventricles, which are hollow regions in the brain, and then it travels along the spinal column, which is located around the spine. By doing so, it safeguards the central nervous system, provides it with nourishment, and eliminates waste products.

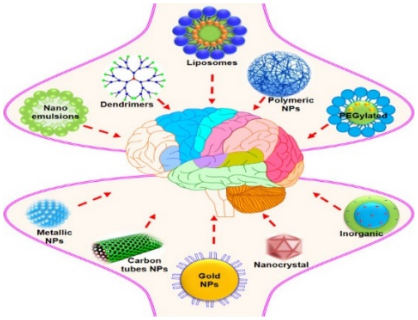

Figure 1: The application of nanotechnology-based medication delivery devices to the treatment of central nervous system problems

Clinical trials that make use of drug delivery systems that are based on nanoparticles are now being carried out, and it appears that these systems have a great deal of potential for the treatment of a

range of illnesses that impact the central nervous system [3]. However, greater research is required in order to increase the scale of manufacturing, conduct safety evaluations over a longer period of time, and acquire a deeper comprehension of the ways in which the BBB interacts with one another.

In spite of these obstacles, developments in nanotechnology and our increasing knowledge of disorders that affect the central nervous system together present a huge opportunity to enhance the results of treatment and satisfy a medical need that has not yet been met.

I. DESIGN OF NANOTECHNOLOGY – BASED DRUG DELIVERY SYSTEMS

To deal with the take-up of pharmaceuticals that are ineffectively soluble, the focusing of drugs to a specific district, and the bioavailability of drugs, nanoparticles can be used in designated drug conveyance at the site of disease. A comparison of untargeted and designated drug conveyance systems is depicted through a schematic representation in Figure. Nanomaterials have been successfully used in the definition of various enemy of disease medications, including paclitaxel, doxorubicin, 5-fluorouracil, and dexamethasone by the drug industry [4].

To encapsulate dexamethasone, a glucocorticoid that acts at an intracellular site of activity, nanoparticles based on polylactic/glycolic acid (PLGA) and polylactic acid (PLA) have been created. Dexamethasone is a chemotherapeutic prescription that has the capacity to block the expansion of malignant growth cells and lessen irritation. Following the restricting of the medicine to the cytoplasmic receptors, the drug receptor complex is then transferred to the nucleus, which at last leads to the production of specific genes that direct the multiplication of the cell. The development of vascular smooth muscle cells was entirely stopped by this medication loaded nanoparticle formulations, which released greater quantities of the medication over a longer timeframe.

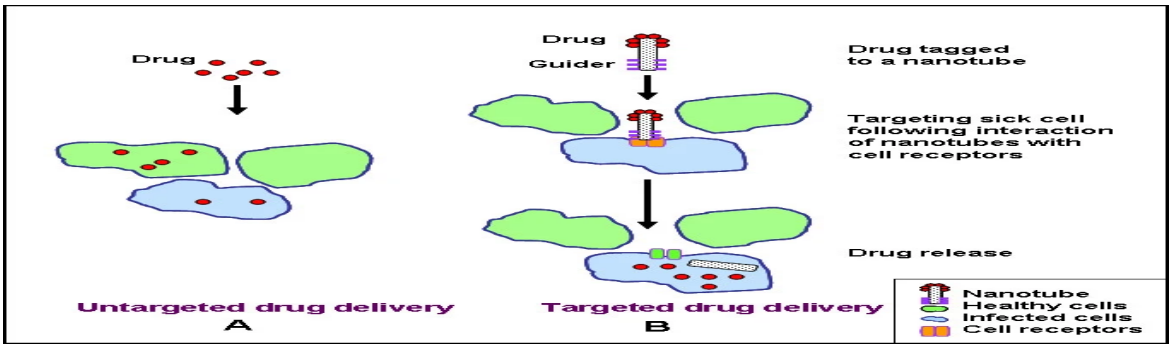

Figure 2: System design for nanotechnology-based medication delivery

To choose if they could be used in cancer therapy, colloidal drug conveyance mechanisms such as liposomes, micelles, or nanoparticles have been subjected to extensive research. The efficiency of medicine conveyance systems can be connected with their minimized size, diminished drug harmfulness, managed time release of the prescription, and variation of prescription pharmacokinetics and natural distribution. These factors all add to the effectiveness of these systems [5].

Most of the time, chemotherapy is not successful in alleviating cancer because some development cells gain resistance to various anticancer medications simultaneously. Whenever cancer cells start to express a protein known as p-glycoprotein, which is equipped for siphoning anticancer medications out of a cell as quickly as they cross through the cell's outside layer, resistance is regularly evolved. This is the case in most of cases [6]. It has been demonstrated in continuous studies that nanoparticles can possibly convey anticancer medications into cells without causing the p-glycoprotein siphon to be enacted.

A study was guided by the researchers to investigate the effectiveness of paclitaxel stacked nanoparticles in human colorectal tumors that were resistant to paclitaxel. In a human colon cancer cell line (HCT-15), it was demonstrated that paclitaxel that was encapsulated in emulsifying wax nanoparticles demonstrated the capacity to beat drug resistance. Through the process of conjugating paclitaxel with albumin, possible to eradicate the insolubility issues are associated with this medication. For the treatment of breast cancer, an injectable nano-suspension called Abraxane has been approved. This nano-suspension contains paclitaxel that has been linked to biocompatible proteins like albumin.

Cremophor-EL, the solvent that was utilized in earlier formulations of paclitaxel, is responsible for causing acute hypersensitivity reactions. Patients are need to go through pre-medication with steroids and antihistamines prior to getting paclitaxel. Additionally, the medication must be administered through gradual infusions that go on for a couple of hours [7]. This is finished to limit the likelihood of allergic responses happening. Because paclitaxel was bound to albumin, a greater quantity of the medication was delivered in a shorter amount of time; this was the impact. As a result of the absence of solvents, toxicities that are associated with solvents are also disposed of. In the clinical preliminary that was driven during Phase III, the response pace of Abraxane was roughly two times as high as that of the prescription Taxol, which contained a solvent.

II. TYPES OF NANOPARTICLES DELIVERING DRUGS TO CNS:

The movement of drugs to the focal nervous system requires nanotechnology. Because of their nano size, these biodegradable and biocompatible nanoparticles can pass through the blood-brain barrier (BBB). Furthermore, their surfaces can be easily modified to maximise the compatibility of the drug with the drug to be loaded. The nanoparticle is composed of two facets:

One encapsulates the medication so order to prevent it from being broken down by enzymes, targets brain cells, crosses the blood-brain barrier, and then releases it at a pH that has been determined. Additional component: the nano-engineered complex.

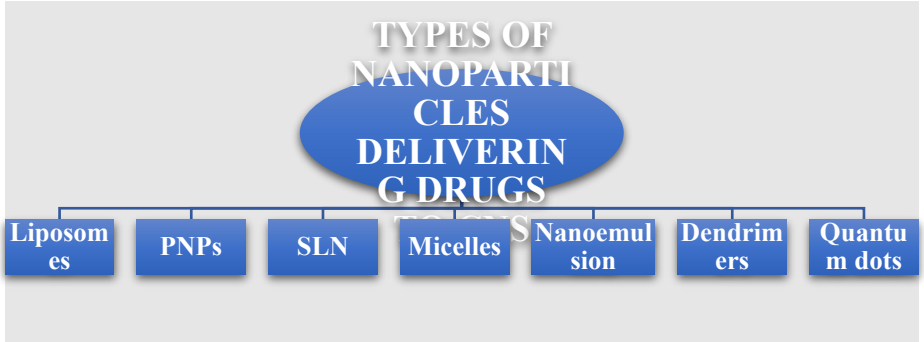

Figure 3: Different types of nanoparticles are used to deliver drugs to the central nervous system

Nanoparticles might possibly transmit medications across the blood-brain barrier by a process that is site-specific, which is one of the advantages of using nanoparticles. Following research including rats, it was seen that as poly (butyl cyanoacrylate) nanoparticles had the decision to lessen the phenytoin resistance that was associated with P-gp. There are numerous varieties of nanoparticles, all of which possesses a distinct composition and serves a changed capacity. Micelles, dendrimers, liposomes, solid-lipid nanoparticles (SLNs), and polynucleotide nanoparticles (PNPs) are among examples [8].

i. Liposomes:

This type of vesicle, known as a liposome, is of the first generation and is spherical in shape. It contains colloidal particles. Because of the hydrophilic components and core lipid bilayers that they include, which give them a morphological similarity to cell membranes, they are suitable for use in the administration of drugs. Small unilamellar (ranging from 10 to 50 nm), multilamellar (ranging from 20 to 100 nm), and huge unilamellar (ranging from 50 to 1000 nm) are the three major categories that we are able to put them into after considering their size and the number of bilayers that they include.

As a result of their capacity to traverse the blood-brain barrier and convey a substantial amount of prescription to the growth, liposomes can possibly be used in the therapy of brain disease. Doxorubicin, erlotinib, 5-fluorouracil, paclitaxel, and methotrexate are just a few examples of the anti-cancer medications that have been introduced into the body through the use of liposomes in a variety of research projects.

The limit of the liposome to cross the blood-brain barrier can be managed in numerous ways. It was discovered that the span of time that the BBB passage

circumnavigated was lengthened when liposomes were covered with several molecules, such as poly (ethylene glycol). Furthermore, the usage of transferrin as the focusing on receptor resulted in an increase in the translocation of the transporter across the blood-brain barrier. Furthermore, the joining of the glucose-L-ascorbic acid complex resulted in an increase in the amassing of liposomes at the objective region [9].

ii. PNPs:

PNPs are compotes of colloidal polymers that are both biocompatible and biodegradable respectively. It is the lipophilic medicine that encloses the dense polymer matrix in the centre that provides the nanoparticles with steric stabilization. It is possible to encapsulate the medication, submerge it, or chemically attach it to the surface in order to successfully administer it.

Polymers such as poly (ethylene imine), chitosan, lactide-co-glycolic acid, poly(allylamine) hydrochloride, and others are frequently utilised in the manufacture of nanoparticles for the purpose of brain administration. A preliminary coordinated in vitro demonstrated that PNPs can possibly be used in the treatment of Alzheimer's disease (Promotion), upgrade of curcumin conveyance to the brain, and decrease of oxidative stress, irritation, and plaque development. An extra investigation demonstrated that their deadly effects on threatening cells were accomplished by propelling the successful assimilation of doxorubicin in human glioma cells all through the study.

iii. SLNs:

SLNs are colloidal mixtures of lipids that are aqueous in nature. These lipids include fatty acids and triglycerides. After being dispersed throughout a solution, these nanoparticles have the potential to solidify when they reach a certain temperature. With the characteristics of low cytotoxicity, physical stability, and the ability to resist drug changes, SLNs are currently being studied for the purpose of administering medication to the brain.

Both hydrophilic and lipophilic drugs are capable of being encapsulated in SLNs. Furthermore, because the encapsulated pharmaceuticals are more stable in SLNs than they are in PNPs, it is possible to achieve a prolonged release profile that can last anywhere from months to years. The active pharmaceutical component is protected from oxidative, chemical, and photochemical degradation by SLNs, which immobilize it within the formulation, so producing a stable state.

This is in contrast to PNPs, which prevent leakage and shield the active pharmaceutical ingredient from degradation. Hydrophobic drugs are thought to have greater bioavailability when they are manufactured as SLNs as opposed to PNP encapsulation. This is attributed to the physiological stability of the lipids.

iv. Micelles:

Micelles are molecules that are stable and amphiphilic. They can be polymeric or non-polymeric according to their size, which can range from 5 to 50 nanometers [10].

The core-shell structure of these molecules is comprised of an inner hydrophobic core that is made up of fatty acids, polypropylene glycol, and polycaprolactone, and an outer hydrophobic core that is made up of polyethylene glycol (PEG).

The micellar strategy allows for the movement of chemicals that are not significantly water-soluble, as well as controlled release, further developed drug bioavailability, and the upkeep of prescription stability. With regards to brain therapy, they can chip away at the distribution of drugs across the blood-brain barrier (BBB). Because of the way that block copolymers like poly (ethylene glycol)- b-poly (lactic corrosive), distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy poly (ethylene glycol), and poly(styrene)- poly (acrylic corrosive) have demonstrated increased absorption, polymeric micelles also might possibly be used as vehicles for the movement of drugs.

v. Nanoemulsion (NE):

Colloidal systems are a sort of system that are often made up of water, surfactant, and edible or culinary oils. NEs are a type of colloidal system. They have a wavelength that ranges from 100 to 500 nanometers. They are promoted as pharmaceutical delivery devices in order to address a number of concerns, including poor identifiability and BBB penetration, among other problems.

In addition to being less soluble in water, NEs are less stable when subjected to varying temperatures, salinities, and pH levels. On top of that, the onset of their influence is rather low. The use of NEs is recommended for the delivery of medication through the nose because of this reason.

vi. Dendrimers:

Both their pharmacological flexibility and their organisation are well-known characteristics of dendrimers. New polymeric structures can be classified into a variety of "generations." Dendrimers have seen significant changes in component materials, branching, and complexity over the course of their evolution. Because of their capacity to transport drugs in both hydrophilic and hydrophobic environments, dendrimers such polypropylene imine, polyamidoamine (PAMAM), and poly-l-lysine are generally used. It is possible that these dendrimers pose a threat because of the negatively charged biological membranes and cationically charged surfaces that they possess.

It is preferable to treat brain illnesses with PAMAM dendrimers. Alzheimer's disease has been treated with carbamazepine. In addition, PAMAM dendrimers combined with PEG have the potential to cure ischemic stroke by delivering medication and lowering the volume of blood that solidifies. One study was able to successfully deliver medications across the blood-brain barrier by utilising generation 6 (G6) hydroxy PAMAM dendrimers that had a high dendrimer accumulation.

This level of dendrimer accumulation is associated with factors that cause inflammation. Microglia and neuronal cells

that had been damaged were the targets of these dendrimers. The treatment for cerebral palsy consisted of decreasing neuroinflammation and analyzing dendrimer uptake as well as the severity of the condition. Extender of Capmul has the potential to improve brain absorption as well as the creation of N-acetyl-l-cysteine-conjugated dendrimers for the treatment of neuroinflammation [11].

vii. Quantum dots:

The semiconductors that are nanoparticle-sized are referred to as quantum dots, or QDs for short. Superfine is the term used to describe their diameters, which range from 2 to 10 nm. They display a wide range of electrical and optical properties, such as the ability to be tuned to a certain size, a high quantum yield, photostability, dazzling light and fluorescence emission, and high emission. Because of these qualities, QDs are the most effective medication ever developed for conditions that affect the central nervous system.

The imaging of brain diseases and diagonals frequently make use of certain conjugated quantum dots. Neither the size nor the chemo-electric properties of these semiconductors have any impact on the base band barrier. For quantum dots (QDs), the surface is the most important factor that enables them to cross through the BBB. In their study, Lien and colleagues demonstrated that graphene quantum dots (QDs) had the ability to inhibit the buildup of Aβ1-42 peptides. Furthermore, they presented a variety of prospective therapy solutions for this particular issue.

There are three types of QDs:

Inorganic QDs: They possess a spectrum of absorption that is continuous;

Carbon-based QDs: A high water solubility, biocompatibility, catalytic capabilities, and surface chemical changes are all characteristics of these substances;

Perovskite QDs: There is luminescence in these materials, in addition to the fact that they are semiconductors.

In order for quantum dots (QDs) to be able to pass through the blood-brain barrier (BBB), they must first be connected to specific molecules. There are a number of different methods that can be utilised to accomplish this. However, there are also extremely rare outliers, such as carbon dots or CDs. Passivation is applied on the surface of CDs, and their size is smaller than 10 nanometers. The production of these dots requires the pyrolysis of l-aspartic and d-glucose as a prerequisite. The CDs undergo a significant transformation as a result of this pyrolysis, which permits them to exert an influence on C6 glioma cells present in the brain. Because of their one-of-a-kind characteristics, CDs have a promising future in the field of medicine [12].

These characteristics include biocompatibility, high adherent fluorescence, and an uncomplicated fabrication method. Because of their huge surface area and excellent dispersity, Fe2O3@CDs, which are a form of core-shell nanoparticle, are frequently used for the delivery of drugs. Their structure is made up of a shell and a core.

III. NANOPARTICLE-BASED TREATMENT OF DISEASES OF THE CENTRAL NERVOUS SYSTEM (CNS) IS NOW UNDERGOING SIGNIFICANT RESEARCH ADVANCEMENTS:

i. Nanoparticles for Alzheimer's Disease:

One of the most common forms of dementia among the senior populace is Alzheimer's disease (AD), which is described by the deposition of amyloid-β (Aβ) peptides in the brain. The process of cloning the quality that encodes the β-amyloid precursor protein (APP) and its subsequent restriction to chromosome 21 has been shown to be associated with the deposition of Aβ, an essential occasion in the etiology of Alzheimer's disease (AD). APP quality alterations have also been discovered to affect the gathering of Aβ, mostly in regions that are not situated inside the brain parenchyma.

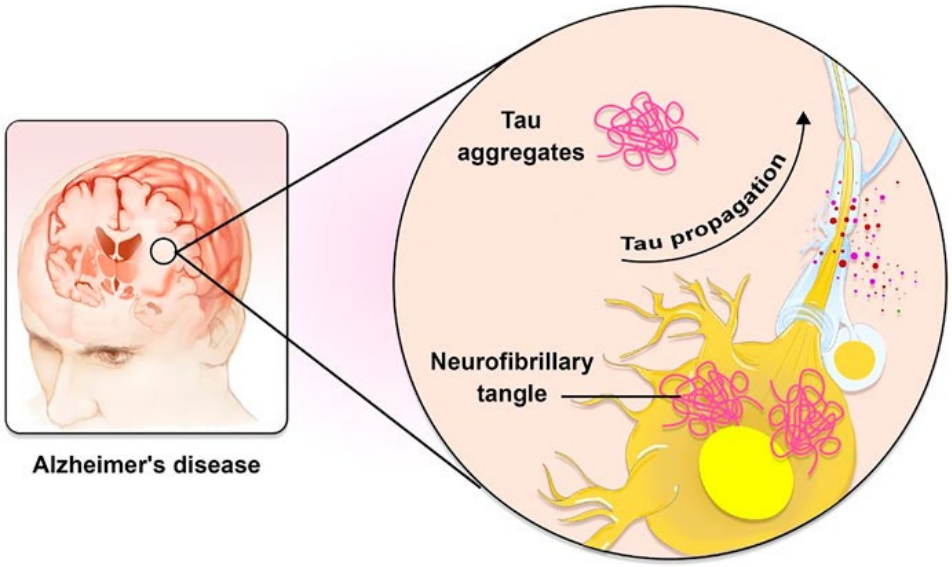

Figure 4: Nanoparticles for Alzheimer's Disease

The creation of plaques in the brain, which are generated by the accumulation of Aβ peptides via accumulation, is a significant clinical hallmark that separates Alzheimer's disease (AD) from other forms of dementia. One reason for the creation of a clever therapeutic strategy is that there is a mismatch between the development of Aβ and its clearance. The procedure in question is established on the utilization of the peripheral-sink impact, which is planned to decrease the quantities of soluble Aβ assemblies present in the cerebral blood vessels and the brain. Each and every mutation that occurs in the Pgp quality has the potential to lead to the formation of β-amyloid plaque, which is the primary factor that leads to the onset of Alzheimer's disease (AD). One reason for this is that β-amyloid is a naturally happening substrate of Pgp.

To identify Alzheimer's disease (AD) at an earlier stage, it is possible to generate nanoparticles (NPs) that possess a specific affinity to actin (Aβ). Magnetic nanoparticles (NPs) have been delivered by Nasr and colleagues. These NPs are coated with sialic acid and contain bovine serum albumin (BSA) [13]. The nanoparticles in question demonstrate a remarkable degree of selectivity with regards to their ability to attach to Alpha deposits. Inside an animal model of Alzheimer's disease (AD), this NP-BSAx-Sia possesses the capability to cross the blood-brain barrier, so facilitating the usage of magnetic resonance imaging (X-ray) to recognize Aβ plaques from the disease.

As a consequence of the metal sinking process, Aβ plaques lead to the development of zinc ions at levels that are a lot greater than those that are observed in the surrounding area. A lack of local zinc, a rise in the expression of favorable to inflammatory cytokines, and a decrease in synapse density are all potential outcomes that could happen as a result of this circumstance. Each of these events has the potential to result in neuroinflammation and death.

The main two active medications that are right now available for the treatment of Alzheimer's disease are memantine and cholinesterase inhibitors. These are the main two drugs that are right now available. Innovative medicines that can either forestall, postpone, or treat the symptoms of Alzheimer's disease are desperately required so that the condition can be forestalled, delayed, or treated.

ii. Nanoparticles for Parkinson Disease:

The neurological disorder known as Parkinson disease (PD) is a condition that affects around two to three percent of persons who are sixty-five years of age or older. Two of the symptoms that are indicative of the illness, which is marked by the death of neurons in the midbrain, are intracellular inclusions and striatal dopamine deficit. Both of these symptoms are present in the condition.

A clinical diagnosis of Parkinson's disease (PD) can be made based on a number of motor symptoms. These symptoms can be utilised to assist in the diagnosis. In addition to bradykinesia, stiffness, tremor, and postural instability, these symptoms also include tremor. In spite of this, there are not a great deal of efforts being made to produce a diagnostic criterion that is accurate [14].

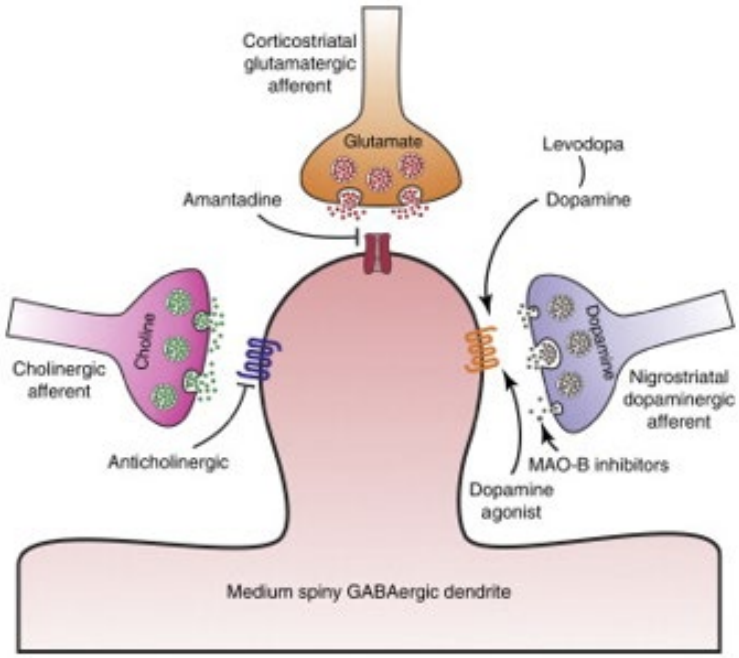

Figure 5: Nanoparticles for Parkinson Disease

The illness has evolved over the course of time as a result of greater understanding of the neuropathology of the disease as well as the molecular and neurophysiological sources of the abnormalities. For the past three decades, levodopa (L-DOPA) has been the most viable medication for treating the symptoms of Parkinson's disease (PD). In any case, levodopa has the potential to create delays in real life as well as a condition that is alluded to as "levodopa-prompted dyskinesia." The development of novel drugs and methods of medication delivery is necessary to enhance the therapeutic efficacy of Parkinson's disease patients and lessen the quantity of unwanted effects they experience.

The enzyme known as monoamine oxidase type B (MAO-B) is considerably inhibited by rasagiline (RSG), which also causes an increase in the levels of dopamine. A recent study examined the effectiveness of composite carriers made of chitosan (CS)-coated poly(lactide-co-glicolide) nanoparticles (PLGA-NPs) in improving the targeting of RSG to the brain. In comparison to the group that received intravenous therapy, the pharmacokinetic findings showed that the Cmax values were higher than the average and that the AUC0–24 was higher. Research carried out in living organisms has proved the significance of providing medications through the intranasal route, as well as the benefits of employing the olfactory administration channel, in order to successfully treat Parkinson's disease and other ailments that affect the brain.

Parkinson's disease (PD) is set apart by a selective loss of dopaminergic neurons,

especially in the substantia nigra pars compacta, and the improvement of intracytoplasmic inclusions known as Lewy bodies that display positive α-syn staining. This is the neuropathological aspect of Parkinson's disease. There are six quality anomalies that are responsible with familial Parkinson's disease, and hereditary research has shed light on these abnormalities. It has been established that novel quality therapies are compelling treatments for Parkinson's disease. One example is a novel inward/external magnetic nanoparticle that carries a shRNA plasmid to disrupt α-synuclein synthesis.

This nanoparticle has the ability to provide both in vitro and in vivo operational repair in a Parkinson's disease model. Using chitosan-modified gold nanoparticles (CTS), another group developed composites with the purpose of binding nerve growth factors to certain cell types. These composites were designed to stimulate nerve growth.

One study found that an intracerebroventricular injection of nanoparticles (NPs) that were loaded with microRNA-124 led to an increase in the number of new neurons that were produced in the olfactory bulb of a mouse that was used to imitate Parkinson's disease. This led to improvements in motor functions as well as the transfer of newly generated neurons into the striatum that had been affected by the injury.

VI. CONCLUSIONS:

Nanotechnology has the potential to generate materials and technologies that offer some extremely intriguing options for the delivery of medication that is selective, patient-focused, and targeted. The design of nanoscale platforms for central nervous system illnesses is more difficult than the design of standard drug delivery systems because of the necessity for exact pharmacokinetics, maximal therapeutic efficacy, minimal side effects, biocompatibility, biodegradability, and biodistribution. While developing a nanostructured or nanosized gadget, it is necessary to take into consideration the specific characteristics of brain tissue. An understanding of the CNS intrinsic barriers, especially the BBB, which refers to the natural defensive structures of the human mind against exogenous and endogenous substances, has been made possible by developments in sub-atomic and cell science as well as current biomedicine. This understanding has considered the information on the CNS intrinsic barriers. With regards to the treatment of focal nervous system illnesses, the usage of nanotechnology, specifically as nanoparticles, presents a fascinating option for the improvement of progressive platforms. Neuroprotective therapies (NPs) have been considered as possibly suitable platforms for the control of symptoms, neuroprotection, or disease regression in Alzheimer's disease and Parkinson's disease. Materials scientists, engineers, and medical care researchers can take significant steps in the discovery of suitable treatments for persistent neurological diseases if they work together [15].

VI. REFERENCES:

[1] Busolo, M. A., & Lagaron, J. M. (2013). Antimicrobial biocomposites of melt-

compounded polylactide films containing silver-based engineered clays. Journal of Plastic Film & Sheeting.

[2] Din, F. U., Aman, W., Ullah, I., Qureshi, O. S., Mustapha, O., Shafique, S., & Zeb, A. (2017). Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *International Journal of Nanomedicine*, 12, 7291–7309. doi:10.2147/IJN.S146647

[3] Faden, A. I., & Loane, D. J. (2015). Chronic neurodegeneration after traumatic brain injury: Alzheimer disease, chronic traumatic encephalopathy, or persistent neuroinflammation? *Neurotherapeutics*, 12(1), 143–150. doi:10.1007/s13311-014-0328-1

[4] Faisal, N., & Kumar, K. (2017). Polymer and metal nanocomposites in biomedical applications. *Biointerface Research in Applied Chemistry*, 7(6), 2286–2294.

[5] Goyal, K., Koul, V., Singh, Y., & Anand, A. (2014). Targeted drug delivery to central nervous system (CNS) for the treatment of neurodegenerative disorders: trends and advances. Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents), 14(1), 43-59.

[6] Hans, M. L., & Lowman, A. M. (2002). Biodegradable nanoparticles for drug delivery and targeting. *Current Opinion in Solid State and Materials Science*, 6(4), 319–327.

[7] Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., et al. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*, 12(2), 207–216. doi:10.1016/S1474-4422(12)70291-0

[8] Kendall, M., & Lynch, I. (2016). Long-term monitoring for nanomedicine implants and drugs. *Nature Nanotechnology*, 11(3), 206–210. doi:10.1038/nnano.2016.17

[9] Lindsley, C. W. (2015). 2014 global prescription medication statistics: Strong growth and CNS well represented. *ACS Chemical Neuroscience*, 6(4), 505–506. doi:10.1021/cn500309b

[10] Modi, G., Pillay, V., & Choonara, Y. E. (2010). Advances in the treatment of neurodegenerative disorders employing nanotechnology. *Annals of the New York Academy of Sciences*, 1184, 154–172. doi:10.1111/j.1749-6632.2009. 05116.x

[11] Mollaamin, F. (2018). The effect of biointerface of chemicals and inhibitors in the cerebral cortex of brain on language cognition. *Biointerface Research in Applied Chemistry*, 8(6), 3628–3634.

[12] Nuriya, M., Shinotsuka, T., & Yasui, M. (2013). Diffusion properties of molecules at the blood-brain interface: Potential contributions of astrocyte endfeet to diffusion barrier functions. Cerebral Cortex, 23, 2118–2126. doi:10.1093/cercor/bhs203

[13] Reynolds, J. L., & Mahato, R. I. (2017). Nanomedicines for the treatment of CNS diseases. *Journal of Neuroimmune*

Pharmacology, 12(1), 1–5. doi:10.1007/s11481-016-9723-4

[14] Riehemann, K., Schneider, S. W., Luger, T. A., Godin, B., Ferrari, M., & Fuchs, H. (2009). Nanomedicine—Challenge and perspectives. *Angewandte Chemie International Edition*, 48(5), 872–897. doi:10.1002/anie.200802585

[15] Sabry, N. M., Tolba, S., Abdel-Gawad, F. K., Bassem, S. M., Nassar, H. F., El-Taweel, G. E., Okasha, A., & Ibrahim, M. (2018). Interaction between nano silver and bacteria: Modeling approach. *Biointerface Research in Applied Chemistry*, 8(6), 35