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An Overview of the Nanoparticles in CNS Targeted Drug Delivery: An Emerging Trend

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Abstract

CNS disorders are growing to be the main concern for the new era of medical industry and the healthcare professionals. There is an increase in the number of patients suffering from CNS disorders day by day. Keeping this data into concern, the main pressure comes over to the medication of the increasing number of the patient compliance for the treatment of the specific CNS disorder. The main basic challenge while treating the specific CNS disorder is the crossing of the drug through the blood–brain barrier (BBB) in an adequate manner and a specific site of action. If the drug crosses the BBB barrier, challenges still standby like, is the drug in the adequate amount to trigger the agonist or the antagonist for the specific disorder. Keeping all these things in mind, this article takes you through the targeted methods of drug delivery with the help of the nanoparticles in consideration to the BBB factors.

Keywords: Nanoparticles; CNS disorders; Blood–brain barrier; Agonist; Antagonist

Abbreviations: BBB: Blood–Brain Barrier; RES: Reticuloendothelial System; CeONP: Cerium Oxide Nanoparticle; LBD: Lewy Body Dementia; HD: Huntington's Disease; GDNF: Glial Cell Derived Neurotropic Factor

Introduction

The major challenge in the treatment of neurorestorative diseases is the interaction of the therapeutic agent with the blood–brain barrier (BBB). Recently, nanomedicines have emerged as a favorable strategy, which leads to transportation of drugs without affecting the normal performance of the barrier. Nanotechnology utilizes solid colloidal particles of nanometer scale (1-100 nm), consisting of polymers or lipids and possessing distinctive architecture, which can be used as drug delivery systems for curing specific diseases. Natural biodegradable polymers which are used, can be obtained from natural sources such as corn, potato, sugarcane or animal sources like chitin, chitosan etc. or can be synthesized by bacteria like polyhydroxybutyrate, polyhydroxybutyrate-co-valerate. Due to the small size of nanoparticles (NPs), they penetrate the tumor tissues to a greater depth with high specificity and have been used for boosting the development of various imaging and diagnostic agents for evaluating the functioning of brain and discovering CNS disorders. Modification of their surface with special ligands including antibodies, antigens or peptides, increases their affinity for the receptors such as low-

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density lipoprotein, transferring and P-gp efflux transporters present on the surface of BBB, thus improving the bioavailability of drugs into brain [1-7]. The advantages of using nanoparticles in drug delivery system are:

- Biodegradable, biocompatible, and non-toxic.
- Physical stability in blood, avoiding aggregation.
- Manufacturing process is scalable and cost-effective.
- Controlled and sustained release of drug at localized site of action, by altering the organ distribution and clearance of the drug.
- Easy manipulation of the particle size and surface characteristics of the nanoparticles for active and passive targeting of drug.
- Modification in the particle degradation property can be done by varying the matrix components.
- Attachment of targeting ligands or stimuli responsive agents can be used to achieve site specific dug delivery.
- Prolongation of the circulation time (PEGylated nanoparticles experience low uptake by phagocyte system when compared to unmodified nanoparticles) [8].

Factors influencing toxicity of nanoparticles

- Nanoparticle shape: Short-rod shaped particles lead to greater cellular destruction as compared to long needle-shaped particles. One of the reasons for cellular deformities is the mechanical trauma due to the sharp edges of particles.
- Nanoparticle size: Particle size and cytotoxicity are inversely proportional to each other. Silver NP of size 10 nm exhibited higher cytotoxicity as compared to particles of size 50 and 100 nm.
- Zeta potential of nanoparticle: Cellular uptake is greatly influenced by the charge distribution on the NP surface. The average charge present on the bilayered membrane of cells is anionic. Therefore, NPs containing cationic charge can easily penetrate the bilayer membrane. Anionic NPs possess low toxicity due to the repulsive forces encountered with the components of cell membrane.
- Aggregation and dispersion status of nanoparticle: There occurs pre-aggregation of NPs, before interacting with the cellular components. This induces accumulation of the membrane receptors, which results in improvement of the amount of energy needed for the uptake of the drug. Monodispersed super paramagnetic iron oxide NPs utilized apoptosis-mediated killing mechanism of the cell and aggregates of micron sized particles acted through oxidative stress mechanism through temperature-dependent autophagy.
- Surface modification of NP'S: Biological response can be changed by altering the surface of NP. Metal NPs were modified with thiol group on the surface, therefore inhibiting aggregation [9].

Types of nanocarriers being used

Lipid NP'S: Due to their lipophilic nature, they have been widely utilized in delivering drugs and genetic material to various cells. These include lipid nanocapsules, solid lipid nanoparticles, stable nucleic acid lipid NPs, and liposomes [10].

Liposomes: Liposomes consist of vesicular form of unilamellar or multilamellar lipid bilayered structure encapsulating internal aqueous compartment [11]. Hydrophilic drugs can be encapsulated in the aqueous compartment of liposome and hydrophobic or amphiphilic drugs can be loaded into lipid bilayer [12]. Conventional liposomes exhibit rapid removal from the blood circulation due to reticuloendothelial system (RES). Modifying the liposomal surface with polyethylene glycol leads to reduction of opsonization of liposomes in plasma, reduction in its recognition and clearance by liver and spleen, and thereby prolonging its blood circulation time and improving therapeutic efficacy in CNS. For example, PEGylated liposomes containing doxorubicin (Doxil) have been approved for ovarian cancer, and metastatic breast cancer treatment [11]. Immunoliposomes can be produced by binding liposomes with MAB. OX26 mab immunoliposome follows receptor-mediated transcytosis across the BBB, without affecting its integrity [6] (Table 1).

Type	Diameter
Small unilamellar vesicles	20–50 nm
Large unilamellar vesicle	100 nm
Reverse phase evaporation vesicle	0.5 mm
Multilamellar large vesicle	2–10 mm

Table 1: Type of liposomes nanoparticles.

Cationic liposome: Encapsulation of the genetic material by the cationic liposomes is a recent advancement in liposomal formulations. It is useful in transporting the genes to the specific target cells and also prevents destruction by the external environment. There is an electrostatic interaction between the positive charge of liposomes and negative charge of DNA, which leads to the formation of lipoplexes. There are two types of cationic liposomes—monovalent and multivalent. They combine with dioleoyl phosphatidylethanolamine (DOPE), thereby improving transfection activity [13]. PEGylation of the LP'S is useful in avoiding the process of opsonization, providing protection from immune response and enhancing the pharmacokinetics [10].

Solid lipid nanoparticles: Solid lipid nanoparticles (SLNs) were developed as an alternative to polymeric NPs, emulsions, and liposomes in controlled drug delivery [3]. They consist of lipid matrix, which is in solid form at room temperature and lack hydrophilic domain.10 They are formulated by physiological lipids including mono-, di-, triglycerides, fatty acids, glyceryl mixtures, and waxes and need surfactants for their stabilization [6]. Their preparation can be done by different techniques such as solvent injection, homogenization method, microemulsification, and solvent emulsification diffusion or evaporation. Due to their small size (10-200 nm), they can easily penetrate the tight endothelial cells of the BBB, escape the reticuloendothelial system and also bypass the liver. Additional benefits include elevated entrapment efficiency and provide release in a controlled manner up to certain weeks [13]. A limitation for SLNs is that the susceptibility to bacterial growth is increased, due to the presence of aqueous phase, which leads to a decrease in stability [10].

Dendrimers: The term "dendrimer" is derived from a Greek word which means resembling a tree [14]. They are globular macromolecules of nanometric scale, with a densely packed surface, having a specific architecture: (1) central core, which can be a single atom or group of atoms; (2) branches emerging from the core; and (3) terminal functional groups [13]. The unique structure of dendrimers granted them with interesting properties such as easy functionalization, versatility, and well-defined reacting groups present on the surface [6]. The most common dendrimers used as drug carrier for hydrophobic and hydrophilic drugs include polypropylene imine, polyamidoamine (PAMAM), and polylysine dendrimers [15]. Conjugation with PEG or carbohydrates led to prevention of toxic effects and enhanced stability in biological system [10]. PAMAM dendrimers have been used most commonly for the delivery of drug as well as genetic material to the CNS. PAMAM dendrimers which are below generation 6 category are removed by kidney filtration or the RES, leading to their rapid clearance from the systemic circulation whereas the PEGylated form or dendrimers which lie above generation 6 category have a long circulation time.

Magnetic NPs: They are composed of elements having unpaired electrons (Ni, Fe, Vo, Cr) in the core, owing to magnetic properties. Iron oxide is the most common core utilized as it has higher stability and is removed by the endogenous iron metabolic pathway, thereby reducing toxicity [10]. Iron oxide nanoparticles are biocompatible and have high biodegradability in vivo, which after metabolizing makes the iron ions to be incorporated in the erythrocytes to form a part of hemoglobin. Presence of external magnetic field or by combining the external magnetic forces with D-mannitol leads to enhancement of the permeability of iron oxide particles across the BBB [6]. Coating the core with polymers, polysaccharides, peptides, phospholipids etc. modulates the pharmacokinetic characteristics, toxicity, and enhances loading capacity. They can be used in therapeutic and diagnostic procedures such as MRI by acting as contrast agents [10].

Polymeric NP: These are solid colloidal particles with drugs being dissolved, entrapped, chemically bonded, encapsulated or adsorbed onto the polymeric matrix. It is stated that the circulation time in blood and accumulation in tumor cell can be increased, by sterically stabilizing the nanoparticles, by causing variations in the size of carriers, nature of polymers, and surface characteristics [13]. They show improved bioavailability, systemic stability, increased loading dose, and longer half-life [14]. Khuller and colleagues prepared different formulations by encapsulating anti-tubercular agents such as rifampicin, pyrazinamide, isoniazid and ethambutol with the polymer poly-lactide-co-glycolide and evaluated its efficacy in a murine model for cerebral drug delivery. The results showed that a single dose was able to maintain sustained level of drug for 5–8 days in plasma and 9 days in the brain. On being compared with free drugs, it showed improvement in the mean residence time as well as relative bioavailability [13]. Chitosan nanoparticles are useful in delivering amyloid-beta subfragments (peptide), dopamine, and caspase inhibitors systemically in the CNS. On coating the NPs with Tween-80, improvement in gallic acid brain targeting as well as targeting profile of drug was observed [6]. Synthetic polymeric NPs consist of polylactic acid, polyglycolic acid, and poly (methymethacrylate), which are useful in gene and drug delivery [5].

Benefits of different nanocarriers in CNS disorders

Treatment of Alzheimer's disease and schizophrenia using nanoparticles: Therapeutic agents such as donepezil, rivastigmine, galantamine, tacrine, and memantine are administered orally for treatment of AD. But most of them do not reach the brain in complete manner due to partial or total presystemic metabolism. Due to this reason, ingestion of higher drug is required which might lead to adverse effects in the vital organs of the body such as heart, kidney, and liver. The greatest hindrance in treatment of AD is the BBB. It is a physical barrier having tight intracellular junctions, which prevents the entry of all large molecules. Moreover, efflux pumps such as P-glycoprotein is present in high levels,

which removes out the chemotherapeutic agents from the brain.

Cerium oxide nanoparticle (CeONP) is useful in prevention or treatment of neurodegenerative diseases by blocking the production of hydroxyl or superoxide radicals, neuronal death, dysfunctioning of neurons and reducing the loss of dopaminergic transmission or decreasing mitochondrial dysfunctioning in the cell [4]. It also effectively protects cells from amyloid beta-related toxicity by preventing the aggregation of Amyloid beta, therefore extending the lifespan of neurons present in the brain. Kwon et al. utilized phosphonium-conjugated CeONPs as a new strategy for reduction of mitochondrial damage, thereby suppressing the death of neurons in mice [15]. Metal NPs were also used for the diagnosis of AD. Metal ions were conjugated with nanoparticles and were taken up by macrophages associated with inflammation linked with AD. These NPs were then detected by MRI. Gold NPs bind to the amyloid beta aggregation, which confirms their presence in diagnosis of AD and associated dementia. Currently schizophrenia is a well-established neuropsychiatric disease. Nonetheless, the treatment of this disorder is not unanimous and fully effective. As a consequence, several approaches have been studied to improve patient's conditions. In this context, the development of new drug nanodelivery systems to increase drug bioavailability and reduce adverse effects has been claimed as a good option.

Treatment of Parkinson disease using nanoparticle: Parkinson disease (PD) is a progressive neurodegenerative movement disorder, in which patients are not able to control their movement in appropriate manner. Critical nerve cells present in the brain are fired out of control [2] because of the degeneration of the dopaminergic neurons present in the substantia niagra region, dysfunctioning of the mitochondrial and ubiquitin-proteosome system and also oxidative stress [15]. Advantages of nanotechnology in Parkinson's disease:

- Useful in developing sensors which detect the low concentration of different biomarkers and are also helpful in developing affordable diagnostic devices.
- Achievement of high therapeutic efficacy.
- Enhancement of bioavailability across the BBB by making use of different transport mechanisms such as active transport via receptor mediated transcytosis, macrophage mediated passive transport or stimuli responsive movement [7].

A recent study reported that L-DOPA containing nanoparticles and polybutyl cyanoacrylate nanoparticles bound with nerve growth factor cross BBB and cause a reduction in the symptoms associated with PD [15]. Lactoferrin modulated nanoparticles with Glial cell derived neurotropic factor (GDNF) encapsulated showed improved locomotor activity, decrease in the loss of dopaminergic neurons and enhancing monoamine transmitter levels [2]. Gold-doped TiO2 nanotubes were also utilized to detect alpha- synuclein. A new approach to treat PD is the gene therapy. Zhang et al. delivered tyrosine hydroxylase gene along with PEGylated immunoliposome to the transferrin receptor in the rat's brain. This technology normalizes the tyrosine hydroxylase activity in the striatum. Intranasal administration has a faster onset of action and decreased systemic toxicity for transporting the drugs to the brain. Odorranalectin (bioadhesive) functionalized PEG-PLGA nanoparticles containing Urocortin showed improved brain uptake and therefore improvement in therapeutic efficacy of drug. Pilay et al. demonstrated that the intracranial implantation of dopamine loaded alginate scaffold embedded cellulose acetate phthalate NP was increased and sustained, having less peripheral side effects in the cerebrospinal fluid of rat when compared to oral administration of L-DOPA [7].

Treatment of prion disease using nanoparticle: Prion disease (PrD) is a fatal neurodegenerative diseases, occurring as a result of accumulation of prion protein present, leading to dementia and motor dysfunction. The first prion disease to be identified in man was Creutzfeldt-Jakob disease. The healthy cellular isoform (PrPC) consists of two alpha helix structures whereas the pathogenic isoform (PrPSc) form amyloid aggregates which are toxic. The therapy followed for Prion disease utilizes different polyamine dendrimers for the removal of the pathogenic form (PrPSc) from the damaged cells by causing lysosomal destruction. Since the activity of polyamines depends on positive charges, this lead to the development of polyamines that were permanently charged and were less toxic. A study revealed that Silver nanoparticle with two functional groups, including sulfonates and primary amines, on their surface were able to degrade the accumulation of PrPSc within the neuroblastoma cells [13]. Calvo and colleagues reported the use of PEGylated polyacrylate nanoparticles as vector for the delivery of the drug in a model having prion disease [4].

Treatment of Lewy body dementia using nanoparticles: Lewy body dementia (LBD) is a neurodegenerative disease, characterized by appearance of Lewy bodies which contain alpha synuclein protein aggregates in the affected neurons. Major difficulties associated with the disease are movement impairment, emotional stress, inability to perform daily activities and repetitive actions, and behavior. The standard treatment for reducing the symptoms of LBD includes cholinesterase

inhibitor, which initially were developed for AD but proved to be responsive for LBD patients. Rivastigmine, a cholinesterase inhibitor showed remarkable results in treating cognitive, functional and neuropsychiatric impairments in LBD. Motor impairment was treated with Levodopa, which is a PD therapeutic agent. PAMAM (Polyamidoamine) dendrimer led to the inhibition of fibril formation in alpha synuclein, serving as a potential therapeutic strategy for LBD treatment [2].

Treatment of Huntington's disease using nanoparticles: Huntington's disease (HD) is a genetic neurorestorative disease whose symptoms include anxiety and involuntary motion. Curcumin loaded solid lipid nanoparticles (SLN-Cur) were explored for their neuroprotective efficiency in a rat model suffering from 3-nitopropionic acid induced HD. It showed the ability of restoring glutathione levels, decreasing reactive oxygen species, lipid peroxidation, and ultimately improving motor coordination.

Treatment of depression using nanoparticles: Several studies have been conducted on examining the possibility of synthesis of a nano-based system for targeted drug delivery that would include antidepressant drug as its integral part. In 2000, Darius et al. [16] published a study on mouse brain tissue kinetics of valproic acid associated with dextran-stabilized and polysorbate 85-coated nanoparticles. It was concluded that nanoparticles may help in reduction of potentially toxic metabolites of valproate. Choudhary et al. have recently demonstrated that it is possible to design and produce a nanoparticle drug delivery system for water soluble antidepressant mirtazapine which belongs to the class of mixed serotonin/nor adrenaline reuptake inhibitors [17].

Conclusion

The medical world is witnessing tremendous advancements in the targeted drug delivery for different CNS associated disorders. Several studies have deduced the role of nanoparticles in targeted drug delivery systems for the therapeutic treatment of neurological disorders. With this article, the authors want to convey the use of nanoparticles in drug delivery systems, their role in the CNS targeted drug delivery, and different nanoparticle techniques, in a more concise form.

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