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Nanotechnology-Based Targeted Drug Delivery for Treatment of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative disorders are becoming prevalent with the increasing age of the general population. A number of difficulties have emerged for the potential treatment of neurodegenerative diseases, as these disorders may be multi-systemic in nature. The drugs with large particles cannot be delivered to brain owing to lack of the functional platform for drug targeting. To overcome this issue pharmaceutical innovation is advancing producing the nanoparticles. Nanomedicine (nanoparticles) is one of the approaches to overcome these issues. Various nanostructure including liposome's polymers, Dendrimers, silicon or carbon material has been detected as well as tested as carriers in drug delivery system. Each of these is promising tools for the delivery of therapeutic devices to the brain via various routes of administration, particularly the intranasal route. Nanotechnology-based treatment, prophylaxis, and adjunctive therapy options are considered promising avenues for the treatment of CNSDs. Nanotechnology research focusing on the CNS will benefit from improvements in neurophysiology, neuroanatomy, and neuropathology. The objective of the present review is to focus on various nanotechnology-based drug delivery systems for the treatment of neurodegenerative diseases.

INTRODUCTION:

Neurodegenerative disorders are becoming prevalent with the increasing age of the general population. A number of difficulties have emerged for the potential treatment of neurodegenerative diseases, as these disorders may be multi-systemic in nature. Due to limitations regarding the blood-brain barrier (BBB) structure, efflux pumps, and metabolic enzyme expression, conventional drug delivery systems do not provide effective therapy for neurodegenerative disorders. Nanotechnology can offer impressive improvement of the neurodegenerative disease treatment by using bio-engineered systems interacting with biological systems at a molecular level[1].

Drug delivery to the brain is always a challenging task for the formulation scientists because of low permeation due to the presence of blood-brain barrier (BBB) with tight junctions in the brain endothelial cells. Even though numerous traditional approaches such as prodrugs, disruption of the blood-brain barrier have shown some success to overcome these challenges, researchers are continuously working on alternatives for better delivery of drug to the brain. Recent advances in nanotechnology offer an appropriate solution for the drug delivery problems associated with the brain-targeted drug delivery. The present review describes various nanotechnology-based formulations such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, Dendrimers, miscelles and Nanoemulsions which have been widely used for the better delivery of the drugs across the blood-brain barrier. It has been estimated that more than 98% of CNS active drugs coming out of synthetic pipelines are not able to cross the blood-brain barrier sufficiently to achieve therapeutic drug concentration[2].

These traditional approaches are less successful to cross the BBB for better brain delivery and most of them are associated with numerous adverse effects. Moreover, some of these approaches are highly destructive in nature which is extremely harmful to the body in long term. Thus, it is a challenge to enhance drug permeability to the brain for effective therapeutic efficacy with no or limited side effects and with better patient compliance[3, 4.]

The most straightforward option is the delivery of AD drugs using nanoparticles. These need to be able to cross the blood-brain barrier (BBB) and reach pharmacologically relevant levels. Nano-mediated drug delivery approaches for Tacrine and Rivastigmine have delivered promising results in the recent years using different routes of delivery and different

nanocarrier systems. A summary of different nano-carrier systems used was published by Fonseca-Santos et al. 2015[5].

Nanoparticle Drug Targeting to the Brain Neurological illnesses is an imperative reason for mortality and constitutes 12% of aggregate deaths around the world [6]. Among the neurological conditions, Alzheimer and different dementias are assessed to constitute 2.84% of the aggregate deaths, while cerebral vascular illness constitutes around 8% of the aggregate deaths in high-income nations in 2005[7]. In these above capacities, it has been clear that nanoparticle is effectively focused to the brain if it effectively crosses the blood-brain barrier (BBB), and it will be lipid soluble, for the most part, dynamic in passive diffusion [8-10]. It should be noted that NPs are articles measured at 1 nm and 100 nm that work all in all unit as far as transport and properties. In this way, nanotherapy is one of the imperative treatments to minimize the rate of mortality in CNS ailments in all over world[11, 12.]

Nanoparticle focused on the brain in taking strides: Nanoparticle drug concentration expanding the inside, or at the luminal surface of BBB cells, building up a locally high concentration gradient amongst blood and brain, higher than that realistic after systemic administration of the free medication The gradient ought to then support the improved passive diffusion of the medication[13-16]. With respect to illustration, this undertaking could be acknowledged by integrating NPs functionalized to target brain slender endothelial cells. This feature can be taken after or not by their consequent uptake from focused cells[17]. By entering into the CNS, nanoparticles carry the medication. This assignment can be acknowledged empowering NPs focusing on brain thin endothelial cells and their ensuing transcellular entry over the BBB[18-21].

Nanoparticles:

Nanospheres and nanocapsules that can be either amorphous or crystalline. Nanopowders are agglomerates of ultrafine particles, nanoparticles or nanoclusters. They are specifically designed to absorb or encapsulate a drug, thereby protecting it against chemical and enzymatic degradation, for targeting particular organs/tissue and also as carriers of DNA in gene therapy, to deliver proteins, peptides, and genes by the oral route. It focuses on the production of nanoscale particles or molecules to enhance the bioavailability of a drug. It also focuses on maximizing bioavailability and for a prolonged period of time. The advantage is

that cells can take up the nanoparticles because of their incredibly small size, avoidance of macrophage clearance, long resistant times.

Biomedical application of nanoparticles[22]:

- Iron oxide nanoparticles can use to improve MRI images of cancer tumors. The nanoparticles are coated with a peptide that binds to a cancer tumor once the nanoparticles are attached to the tumor the magnetic property of the iron oxide enhances the images from the Magnetic Resonance Imagining scan.

- Nanoparticles coated with proteins that attach to damaged portions of arteries. This could allow delivery of drugs to the damaged regions of arteries to fight cardiovascular disease.

- Quantum Dots (crystalline nanoparticles) that identify the location of cancer cells in the body.

- Gold nanoparticles that allow heat from infrared lasers to be targeted on cancer tumors.

- Porous silica nanoparticles used to deliver chemotherapy drugs to cancer cells.

- Nanoparticles, when activated by x-rays that generate electrons that cause the destruction of cancer cells to which they have attached themselves. This is intended to be used in place radiation therapy with much less damage to healthy tissue.

- A nanoparticle cream that releases nitric oxide gas to fight staph infections.

The application of nanotechnology for the drug delivery to the brain opens the doors of opportunities for the formulation scientists for the better and selective brain delivery of existing and newer potential molecules with CNS activity. It has been assumed that the delivery to a brain of a majority of the potential CNS drugs which have the inability to cross BBB could be modified by nanotechnology in order to achieve better therapeutic action and better patient compliance. It would bring about rebirth to many drugs which have been discontinued due to their failure to gain therapeutic concentration in the brain.

Mechanism of the delivery of nanoparticulate formulations across the BBB[23-24]

Describe the number of possibilities that could explain the mechanism of the delivery of nanoparticulate formulations across the BBB.

1. As compared to the pure drugs, there is an increased retention of the nanoformulations in the brain blood capillaries combined with more adsorption to the capillary walls. These retention and adsorption create a higher concentration gradient that would enhance the transport across the endothelial cell layer and result in better delivery to the brain.

2. The nanoparticles could lead to an opening of the tight junctions between the brain endothelial cells. The drug could then permeate through the tight junctions in either free form or as nanoparticles in bound form.

3. There is a general surfactant effect of nanoformulations characterized by solubilization of the endothelial cell membrane lipids that would further lead to membrane fluidization and thereby enhanced drug permeability through the blood-brain barrier.

4. The nanoformulations may be endocytosed by the endothelial cells of the brain capillaries which would further result in the release of the drugs within these cells and delivery to the brain.

5. Drug-loaded nanoformulations could be transcytosed through the endothelial cell layer.

6. The surfactant which is used as the coating agent could inhibit the efflux system, especially P-glycoprotein (Pgp). Endocytosis via the low-density lipoprotein (LDL) receptor, mediated by the adsorption of apolipoprotein B and/or E from the blood is also a suggested mechanism for the nanoformulations coated with polysorbate such 13- as Tween 20, 40, 60 and 80, and poloxamers such as Pluronic F68.

Table No. 1: Nanoparticle Formulation and Its Advantages

Formulation	Advantages
Polymeric nanoparticles	• Selective distribution of higher brain permeability[25] • Increased the extent of drug permeation to brain [26] • Better brain uptake, higher direct transport percentage[27] • Drug concentration in mice brain greatly enhanced, reduced the toxicity of AmB to liver, kidney etc.[28] • Augmented accumulation of NP in the tumor site and in the contralateral hemisphere.[29]
Solid lipid nanoparticles/ Nanostructure lipid carriers	• Higher affinity to the porcine brain capillary endothelial cells as compared to macrophages.[30] • The AUC and MRT of clozapine SLNs were significantly higher in brain.[31] • Drug and its metabolite were detected in the brain only after IDA-SLN administration.[32] • Brain-targeting efficiency of baicalein was greatly improved by NLCs.[33]
Liposomes	• Liposomes were strongly internalized in cultured cell lines within 6h.[34] • Considerable increase (10-fold) in the bioavailability of the drug in the brain parenchyma.[35]
Dendrimers	• 12-fold greater permeability across porcine brain endothelial cells [36] • Higher targeting efficiency and biodistribution to the brain. [37]
Micelles	• Demonstrated higher drug targeting index (5.20), drug targeting efficiency (520.26%) and direct transport percentage (80.76%).[38]
Nanoemulsions	• Higher drug transport efficiency (DTE %) and increased direct nose to brain drug transport (direct transport percentage, DTP %) [39] • Improved brain uptake. [40]

Nano formulations for Brain Targeting

Polymeric nanoparticles

Nanoparticles (NPs) are colloidal particles, less than 1000 nm that can be used for better drug delivery and prepared either by encapsulating the drug within a vesicle and or by dispersing the drug molecules within a matrix.[41] NPs have significant advantages like better bioavailability, systemic stability, high drug loading, long blood circulation time and selective distribution in the organs/tissues with a longer half-life.

Polymers

Include poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (lactic-co-glycolic acid) (PLGA), poly (caprolactone) (PCL), chitosan, gelatin, and poly (butyl cyanoacrylate) (PBCA). Coating of these NPs with the surfactant polysorbate 80 enables them to cross the BBB by adsorption of apolipoprotein E from the blood, generating low-density lipoprotein mimics, which are taken up by cells of the BBB through receptor-mediated endocytosis[42].

Solid lipid nanoparticles (SLN)

Solid lipid nanoparticles (SLN) are colloidal particles composed of biocompatible/biodegradable lipid matrix that is solid at body temperature and exhibit size in a range of 100 to 400 nm. SLN called nanostructured lipid carriers (NLC), with increased drug loading are also becoming popular recently for brain targeting which is composed of a solid lipid and a certain amount of liquid lipid (oil), maintaining the solid state at both room and body temperature. SLN are taken up readily by the brain due to their lipidic nature.[43-45]

Liposomes

liposomes consist of bilayer phospholipid systems in which water-soluble drugs could reside in the aqueous phase enveloped by phospholipid bilayer and the lipophilic drugs, could directly integrate into the membrane.[46] Targeted brain delivery using liposomal systems resulted in considerable increase of drug concentration in brain/*in vitro* cell lines.[47-48]

Liposomes as nanocarriers with a large transport capacity have been used for drug delivery to the brain. This is because liposomes can encapsulate different components, which are thereby properly protected against degradation by plasma enzymes and elimination by the reticuloendothelial system. Most importantly, liposomes are able to fuse with biological membranes, to be transported across cell membranes by endocytosis, and to penetrate through the BBB.[49] Gobbi et al. (2010) prepared liposomes with an average size of 145 nm that were targeted to Aβ by incorporation of phosphatidic acid and cardiolipin. The high affinity of these liposomes *in vitro* to Aβ oligomers, but not to monomers, suggests that they may be useful for the targeted delivery of diagnostic and therapeutic compounds in animal models of AD and clinical trials.[50]

Dendrimers

Dendrimers are a unique class of synthetic polymers which has a 33 major role in nanotechnological advances in drug delivery. The term "dendra" in "dendrimer" is derived from Greek which means tree and therefore appropriately describes its architecture. Dendrimers, one of the polymeric nanotechnologies building blocks.[51, 52] is macromolecular structures with globular shape and a densely packed surface. Their structure has offered them a number of biomedical potentials. Recently, a multipurpose anti-amyloid strategy was suggested for dendrimers.[53]

Micelles

Polymeric micelles obtained from block copolymers as colloidal carriers for drug and gene targeting have been receiving much attention in the field of drug delivery and targeting because of the high drug-loading capacity.[54] Researchers have demonstrated effective targeting of micelles systems to the brain by intravenous as well as intranasal route.[55]

Nanoemulsions

Nanoemulsions have also gained considerable attention in research as well as in therapeutics due to their advantages such as ease of preparation, thermodynamic stability, optical clarity, and their ability to incorporate both hydrophobic and hydrophilic solutes etc[56]. Intranasal Nanoemulsions based brain targeting drug delivery system of risperidone was studied by Mukesh Kumar *et* 39 *al*. This process uses common biocompatible oils such as triglycerides and fatty acids and combines them with water and surface-coating surfactants. Oils rich in omega-3 fatty acids especially contain important factors that aid in penetrating the tight junctions of the BBB.[58]

CONCLUSION:

The application of nanotechnology in drug delivery has opened various opportunities for the formulation scientists for the better delivery of therapeutic agents to CNS. Numerous drug molecules have been made to be permeated through blood-brain barrier by incorporating in suitable nano-formulations which resulted in enhanced efficacy of the drug and better therapeutic action. Nanotechnology-based treatment, prophylaxis, and adjunctive therapy options are considered promising avenues for the treatment of CNSDs. Nanotechnology

research focusing on the CNS will benefit from improvements in neurophysiology, neuroanatomy, and neuropathology The therapeutic potential of nanotechnology for AD includes both neuroprotective and neuroregenerative approaches. In addition, nanotechnology has shown promising applications in targeted drug delivery for an AD, and several nanocarriers systems have been studied in recent years to increase the bioavailability and efficacy of different AD therapeutic agents. Further research works should focus on nanotoxicological risk assessments, cost-effective assessments as well as the development of biodegradable nanoparticles.

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