Chapter 10
Application and Efficacy of Nanoparticle-Based Therapy Among Neurodegenerative Diseases

M. Vijay Kumar and Kartik Bhairu Khot

Abstract Human body is well known for its central nervous system (CNS) where physiological iteration in the form of any neurodegenerative disease dismays its normal function, voluntarily or involuntarily. The presence of complex tightly packed endothelial cells of blood–brain barrier (BBB) prevents the entry of most of the biologically active molecule into the brain, affirming us the dilemma present and the challenges posed in its treatment strategy. Thus, the current conceptualization delves into the concept of various nanotechnological approaches, their method of preparation and application with a broad view of neurodegenerative diseases, and application of nanotechnology as a therapeutic strategy with prime focus on pharmaceutically engineered dimension of 1–100 nm nanoparticles conferring vivid features alongside multifunctional properties of the special ability to cross BBB.

Keywords Nanoparticle · Neurodegenerative diseases

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
CAG	Cytosine, adenine, guanine
CMC	Critical micellar concentration
CNS	Central nervous system
DDS	Drug delivery system
HD	Huntington's disease

M. V. Kumar (✉)
Department of Pharmacology, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangalore, Karnataka, India
e-mail: vijaykumar@nitte.edu.in

K. B. Khot
Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangalore, Karnataka, India

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2022

P. Elumalai, S. Lakshmi (eds.), *Functional Foods and Therapeutic Strategies for Neurodegenerative Disorders*, https://doi.org/10.1007/978-981-16-6703-9_10

Lt	Lactoferrin
Ltf	Lactoferrin receptor
LUVs	Large unilamellar vesicles
MLVs	Multilamellar vesicles
MWNTs	Multiwalled nanotubes
NDs	Neurodegenerative diseases
o/w	Oil in water
PAA	Polyacrylic acid
PD	Parkinson's disease
PEG	Polyethylene glycol
PVP	Polyvinylpyrrolidone
QDs	Quantum dots
RES	Reticuloendothelial system
ROS	Reactive oxygen species
SLNs	Solid lipid nanoparticles
SOD	Superoxide dismutase
SUVs	Single unilamellar vesicles
SWNTs	Single-walled nanotubes
UV	Ultraviolet

10.1 Introduction to Nanotechnology

Nanotechnology as an allied science inherits the term nano from Latin parlance meaning "dwarf," implicating that the unit size of nano in meter is one thousand-million-meter, i.e., 1 nm $= 10^{-9}$ m. Nanotechnology imbibes an expanded version in the conventional mode of drug delivery system, flaring its application in the area of CNS and tumor targeted delivery with leading edge in gene delivery too (Modi et al. 2010). Thus, nanotechnology as a branch of science deals with the matter of nanoscale length size (Bhatia 2016).

Nanostructures play an important role in the field of pharmacy by eliminating the difficulties associated with dosage forms (Orive et al. 2003; Tiwari et al. 2012). The nanocarrier as a potential medication was recently highlighted as an advanced drug delivery system (DDS) in the field of nanotechnology. The unique physicochemical property and smaller size of nanocarrier provide more surface area, allowing it to pass the impermeable membrane. Therefore, among several strategies being adopted to improve the therapeutic efficacy of pharmaceutical dosage forms, the drug delivery system (DDS) is of primary concerns. DDS as a novel mode in pharmaceutical sciences is capable of providing defense against the rapid clearance of drugs and improving the concentration of drugs at a minimal dose. This is only feasible if there is a variation in the therapeutic or harmful impact of a medicine due to a difference in dose or concentration. Another type of drug delivery system is a cell- or tissue-specific strategy, in which the drug is bound to a carrier that can deliver into

the desired location. In short, although the **marketed** formulation has some effect on reducing the need for effective ND therapy, it has also created a wall of drawbacks including poor distribution, rapid first pass effect, limited efficacy, unfavorable side effects, and nonselectivity in delivering the dosage form to the required site (Kumar et al. 2020a, b; Bhatia 2016). Hence, the goal of drug distribution to the desired place followed by a treatment of neurodegenerative diseases (ND) is of critical concern at present times.

10.2 Classification of Nanoparticles

1. One-dimensional nanoparticles: Thin film or monolayer commonly applicable in the field of solar cell panels, optical fiber, optical devices, and other information storage systems.
2. Two-dimensional nanoparticles: Carbon nanotubes.
3. Three-dimensional nanoparticles: Dendrimer, quantum dots, and fullerenes (carbon 60) (Pal et al. 2011).

10.3 Types of Pharmaceutical Nanosystem

Carbon-based structures: Carbon nanotubes are organized in the shape of a graphite sheet. These buckyball-filled cylindrical structures of nanotubes are hexagonal carbon atoms with a diameter of 1 nm and a length of 1–100 nm (Bhatia 2016). Carbon nanotubes penetrate the cellular membrane by endocytosis mechanism showing their drug targeting capability; hence, they can be used in the development of various pharmaceutical dosage forms with the motive of treating the disease condition (Barron and Khan 2008). Based on their structure and size, carbon nanotubes are divided into two types: single-walled nanotubes (SWNTs) and multiwalled nanotubes (MWNTs). With respect to above-configured types, C_{60} (fullerenes) is another carbon-based structure included in it. Fullerenes are carbon-based hollow cylindrical cage structures, also called buckyballs, and differ by arrangement of graphite cylinder. The size, surface, and geometrical properties of fullerenes are some of the key properties suggesting them as a drug carrier. The diameter of SWNTs and C_{60} fullerenes is in the range of 1–2 nm, whereas the diameter of MWNTs ranges from several nanometers to 10 nanometers having a distance of 0.36 nm between the layers of MWCNTs. The length of these carbon-based nanostructures varies from 1 μm to several micrometers (Reilly 2007). They are concentric forms of nanotubes used as stable drug carriers. They are prepared by laser ablation, chemical vapor deposition, electric arc discharge, or combustion technique.

Quantum dots:(QDs) are semiconducting nanocrystals with a diameter of 2–10 nm that have an inorganic semiconductor core (CdSe) and an aqueous

organic-based shell (e.g., ZnS) covering it, which increases optical properties and emits fluorescence when exposed to light. QDs have a cap that increases their solubility in an aqueous buffer. The color produced by a QD is determined by its core, whereas the outside aqueous shell is required for biomolecule conjugation. Biomolecules that can be conjugated in QDs are the targeted biomarkers essential for the targeted delivery of various therapeutic moiety. QDs' property varies with respect to their size ranging from 2 to 10 nm in radius. QDs are used for intracellular tracking as a nanotheranostic drug delivery system because of their emission, fluorescence, photostability, and UV excitation properties (Bailey et al. 2004; Iga et al. 2007).

10.3.1 Nanoshells

Nanoshells are modified forms of nanoparticles that are formed by a combination of a silica core with a metallic outer coating. The core to shell ratio can be changed to alter their qualities. It can be customized in terms of size, shape, and morphology. Nanoshells are used to create various morphological arrangements, which begin with the use of morphological core particles such as rings, wires, rods, tubes, cubes, and other morphological core particles coated with a thin shell. Nanoshells are utilized for chemical stability, luminescence enhancement, biosensors, and other applications (Bhatia 2016).

10.3.2 Polymeric Nanoparticles

Polymeric nanoparticles are biodegradable biocompatible nanoparticles made up of natural polymer or polymer from synthetic origin. The potential application of these nanoparticles is in tissue engineering, drug delivery strategy, and gene delivery, which is completely based on the biodegradable and biocompatibility of polymer (Guterres et al. 2007). Various advanced natural polymers consist of synthetic polyester like poly(D,L-lactide) or polycyanoacrylate and related polymers like poly(lactide-co-glycolide) PLA or poly(lactid acid) (Parveen et al. 2012). In addition to the above polymers, various natural polymers like gelatin, chitosan, sodium alginate, and albumin are also used to prepare nanoparticles. On the basis of their fabrication method, polymeric nanoparticles are also categorized as nanocapsules or nanospheres. Nanospheres have a matrix core where active moiety gets dispersed and even gets adsorbed to the surface of nanospheres. Nanocapsules have an inner core where active molecules get incorporated and also adsorbed at the surface. Polymeric nanoparticles can attain particles of less size than 100 nm, which is one of the important criteria for brain targeted delivery. Polymeric nanoparticles have lesser circulation time as they get opsonized by the reticuloendothelial system (RES), which is increased by coating them with hydrophilic nonionic polymer like

polyethylene glycol (PEG) that increases their circulation time. This approach improves the circulation time but lacks target specificity, which is improved by conjugation of protein, ligand, or antibodies that can attach to the targeted receptor (Parveen et al. 2012; El-Say and El-Sawy 2017).

10.3.3 Liposomes

Liposomes are novel vesicular drug delivery systems that are fabricated by thin-film hydration techniques. There are several methods by which liposomes can be prepared; among those methods, thin-film hydration is the common one. Liposomes consist of a lipid bilayer encircling the aqueous core. These are the first-generation nanoparticles having a similar characteristic property with the cellular membrane. Phospholipid and cholesterol are the two important components of liposomes where phospholipids form a lipid bilayer while coming in contact with the aqueous solution, and cholesterol increases the stability of the composed bilayer. Liposomes are available in different size ranges; based on their classification, liposomes are categorized as single unilamellar liposomes/vesicles (SUVs), large unilamellar liposomes/vesicles (LUVs), and multilamellar liposomes/vesicles (MLVs). The size of liposomes varies from 100 nm to several micrometers. SUVs are considered as the nanocarrier as their size ranges from 50 to 150 nm (Akbarzadeh et al. 2013). Liposomes are versatile in nature; they can entrap a wide range of molecules irrespective of their properties. Liposomes can entrap both lipophilic and hydrophilic molecules in a single vesicle reducing the risk of nonspecific effects with improved bioavailability. Stealth liposomes are similar to PEGylated polymeric nanoparticles, increase the circulation time of liposomal formulation, and can be fabricated into ligand-modified PEGylated liposomes for targeted delivery (Cascione et al. 2020).

10.3.4 Lipid Nanoparticles

Lipid nanoparticles are also called solid lipid nanoparticles (SLNs). SLNs were used as an alternate therapy to liposomes (nanovesicles), polymeric nanoparticles, and polymeric emulsions. Solid lipids, such as pure triglycerides, complicated glyceride mixes, or even waxes are used in the preparation of SLNs. These lipids are solid at room and body temperature that gives them a prominent name as solid lipid nanoparticles. Surfactant stabilizes SLNs, which increases their characteristics when compared to other nanocarriers. SLNs are biocompatible and biodegradable nanoparticles that can be targeted to the specific site of the body for the treatment of various disease conditions. Targeted delivery in SLNs is achieved by conjugating a ligand on their surface, which is even called stealth SLNs. Stealth SLNs are used to improve the circulation time of nanoparticles and to attain targeted delivery (Parveen et al. 2012).

10.3.5 Polymeric Micelles

Polymeric micelles are the micelles of block copolymer consisting of hydrophilic and hydrophobic monomer units. Preparation of micelles depends upon the amount of block copolymer. An increase in the concentration of block copolymer above the critical aggregation concentration (CAC) or critical micellar concentration (CMC) in an aqueous medium results in the escape of hydrophobic monomer unit aggregate from the aqueous phase to form micellar core structures (Xu et al. 2013). The hydrophobic monomer units of polymeric micelles are a copolymer of lactic acid and glycolic acid, hydrophobic poly(amino acid), and poly(caprolactone), while hydrophilic monomer units are polyethylene glycol (PEG), which is most widely used. Polyvinylpyrrolidone (PVP) and polyacrylic acid (PAA) are used as PEG alternatives. Polymeric micelles have a long circulation time because of their small size and hydrophilic shell, which minimizes their RES uptake. The hydrophilic portion of micelles composed of PEG can be used as a conjugating portion for the binding of specific ligand or targeting molecule. Chemical binding or conjugation of specific ligands increases the concentration of drugs in the organ with the disease state. Polymeric micelles increase the solubility of the poorly soluble drug, which increases the systemic availability of the drug and increases the penetrability of the drug across the biological membrane (Parveen et al. 2012).

10.3.6 Ceramic Nanoparticles

Ceramic nanoparticles contain inorganic materials that are used to encapsulate biomacromolecules for the delivery of the drugs across the membrane. Ceramic nanoparticles protect the biomacromolecules from the altered pH of biological fluids; hence, specific enzymes and other pH-sensitive macromolecules can be loaded on them. Silica, alumina, and titania are the commonly used inorganic materials for the preparation of ceramic nanoparticles as they are inert in nature. Ceramic nanoparticles are smaller in size, and hence it is more effective in evading the RES uptake. The surface of ceramic nanoparticles is conjugated with a specific ligand or antibody in order to have a targeted approach (Parveen et al. 2012).

Apart from the above-mentioned nanoformulations, there are other nanoparticles such as metal nanoparticles and magnetic nanoparticles that have played a significant role in the field of pharmacy. A schematic diagram representing some of the nanoparticles is illustrated in Fig. 10.1.

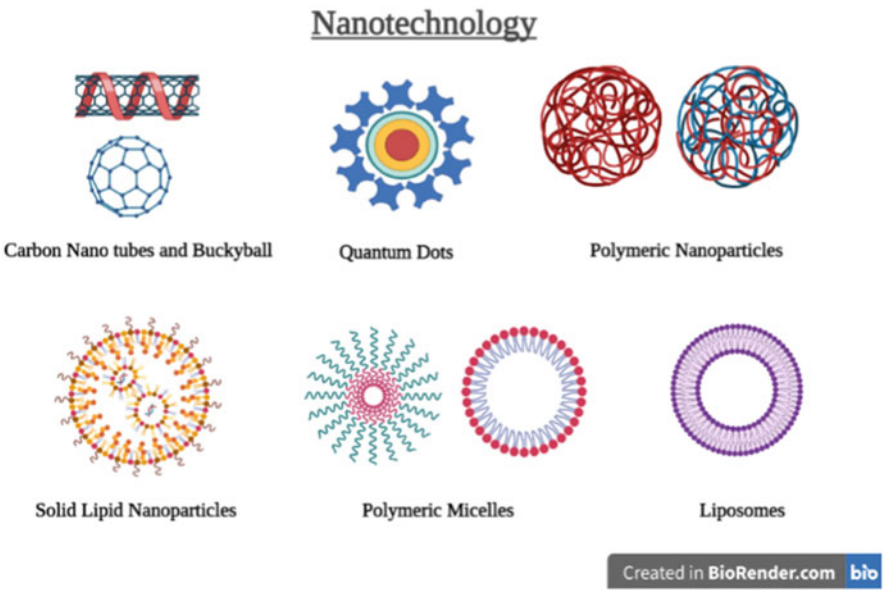

Fig. 10.1 A diagrammatic representation of nanoparticles

10.4 Method of Preparation of Nanoparticles

Depending upon their types, nanoparticles are prepared by various methods. To reduce the size and to confer compatibility according to the biological environment, several polymers are used. Polymers are biocompatible, biodegradable, and nonimmunogenic; hence, based on the types of polymer and drug to be loaded, nanoparticles are prepared.

10.4.1 Solvent Evaporation Method

It is the most extensively used technique for synthesizing nanoparticles. The method follows two steps: first, emulsification of polymeric solution in aqueous phase; and second, removal of organic solvent via evaporation. In this method, hydrophobic medicaments and polymers are dissolved in an organic solvent. The prepared organic solution is emulsified in an aqueous phase containing emulsifying agents or surfactants to form oil in water (o/w) type of emulsion. Emulsion so formed is kept under continuous stirring to evaporate the organic solvent under reduced pressure to form a stable emulsion. The amount and type of stabilizer, polymer concentration, and homogenizer speed were found to influence the size range of nanoparticles. To create nanorange particle sizes, ultrasonication or high-speed homogenization are frequently used. The prepared nanoparticles are centrifuged

and then washed with distilled water to eliminate the remaining stabilizers or free drugs before being lyophilized for storage (Bhatia 2016; Pal et al. 2011).

10.4.2 Diffusion Method

This method is also called as solvent diffusion method. The approach behind this method follows solvent evaporation. In this method, the minimum concentration of water-miscible and water-immiscible solvent act as an oil phase. Interfacial turbulence is created during the spontaneous diffusion of solvents between the two phases, which can lead to the foundation of smaller particles. The concentration of water-miscible solvent can be increased to achieve smaller particle sizes. Drugs that are hydrophobic or hydrophilic can be tested using this method. A multiple w/o/w emulsion with the drug dispersed in the internal aqueous phase is required for hydrophilic drugs (Bhatia 2016; Pal et al. 2011).

10.4.3 Emulsion Diffusion Method

This is yet another popular approach for making nanoparticles. In this method, polymer is mixed in a partially water-miscible solvent and saturated with water. This saturated polymeric solution is emulsified in an aqueous solution containing a stabilizer where diffusion of solvent occurs within the exterior phase. The process of diffusion is based on the oil-to-polymer ratio. Finally, the solvent is removed by evaporation or filtration. There are a few benefits associated with this approach: high encapsulation efficiency (usually 70%), no requirement for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and a restricted size distribution (Bhatia 2016; Pal et al. 2011).

10.4.4 Precipitation Method

Precipitating preformed polymer in an organic solution and diffusing the organic solvent into the aqueous media are the steps in this approach. Diffusion of organic solvents can occur with or without the addition of a surfactant. Polymers, drugs, and some of the lipophilic surfactants are dissolved in a semi-polar solvent like ethanol or acetone. After they have completely dissolved, the solution is poured or injected into an aqueous solution containing a stabilizer while being stirred magnetically. The rapid solvent diffusion produces nanoparticles almost instantly. The solvent is then withdrawn under reduced pressure from the suspensions. The size of the particles is determined by the amount of organic phase added to the aqueous phase. It was also discovered that as the mixing rate of the two phases rises, both particle size and drug

entrapment decrease. This approach is better for medications that are not very soluble. The particle size, percentage yield, and drug release of nanoparticles can be controlled by the optimization of several factors (Bhatia 2016; Pal et al. 2011).

10.5 Neurodegenerative Disease

Neurodegenerative disease is a clinical condition of the central nervous system (CNS) where the normal functioning of neuronal cells gets affected. The pathologies of neurodegenerative disease are different in the case of Alzheimer's, Parkinson's, Huntington's disease, amyotrophic lateral sclerosis, and frontotemporal dementia, while the symptoms associated with it are memory loss, cognitive impairments, behavioral impairments, and adverse events like inability to speak, move, and breathe. The pathological events in neurodegenerative disease include genetic mutation, deposition of abnormal protein, and formation of neurotoxic molecules, all leading to apoptosis. The exact mechanism of neurodegenerative disease is unknown, but above all, pathological events are the hallmark of neurodegenerative disease (Spuch and Navarro 2011; Kumar et al. 2020a, b; Cano et al. 2020).

10.5.1 Common Neurodegenerative Disease

10.5.1.1 Alzheimer's Disease

Alzheimer's disease (AD) is the principal cause of dementia, especially affecting the elderly population. The exact mechanism of AD is unknown, but it is believed that the deposition of senile plaques and neurofibrillary tangles in the extracellular and intracellular region of the brain is the pathological hallmark of AD. Senile plaques are the extracellular amyloid-beta originated from amyloid precursor protein (APP), and neurofibrillary tangles are the hyper-phosphorylated form of tau protein. Deposition of proteins triggers the immune cells to produce pro-inflammatory factors that mainly affects the mitochondria of neuronal cells to produce more amount of reactive oxygen species, which results in oxidative stress and finally neuronal death (Kumar et al. 2015).

10.5.1.2 Parkinson's Disease

Parkinson's disease is a chronic neurodegenerative disease and the second most affecting ailment after Alzheimer's. It is one of the commonly occurring disease, especially in elderly populations. PD is caused by the degeneration of dopaminergic neurons at the substantia nigra pars compacta (SNPC) region of the brain (Kumar et al. 2020a, b). The death of dopaminergic neurons decreases the level of dopamine,

which is the essential neurotransmitter required to transmit signals within the brain cells for normal motor functions. Reduction in dopamine levels induces impaired motor and behavioral functions like stiffness of limbs, tremors, slow movements, difficulty in movements, balance, and coordination. Similar to Alzheimer's, the exact cause for the disease progression is unknown, but it is believed that deposition of Lewy bodies containing α-synuclein protein is the pathological hallmark of PD. α-Synuclein is a protein localized in the presynaptic terminals of the neurons. Increased accumulation of α-synuclein causes toxicity, leading to neuronal dysfunction. Another molecular mechanism revealed the progression of the disease, where cell–cell transmission of α-synuclein increases the onset of disease. Cellular transmission of α-synuclein synergizes the pathological events called synuclopathy that invades all the normal neuronal cells of the brain. This in turn degenerates the neurons of nigrostriatal bundles leading to deficiency in dopamine production (Kumar et al. 2020a, b; Singh and Devasahayam 2020).

10.5.1.3 Huntington's Disease

Huntington's disease (HD) is an autosomal neurodegenerative disease (ND) characterized by defects in motor, behavioral, and cognitive functions. It is an inherited genetic disease of the striatum caused by the expansion of CAG trinucleotide gene expression of the huntingtin gene. The repeated cytosine, adenine, guanine (CAG) trinucleotide sequences of the huntingtin gene are 17–20 in the normal population, which vary in HD-affected patients where the repeated CAG trinucleotide is 40 and more. During the pathogenesis of HD, an increase in the number of polynucleotide sequence above the threshold converts the protein α-helix to the β-folded chain. These chains will coagulate together, representing the structural form of amyloid complexes within the neuronal cells. Aggregation of polyglutamine is initiated by lysis of N-terminal huntingtin protein by caspases, calpains, and other endoproteases, thus exposing the mutant N-terminal fragments that are aggressive against the surrounding substrates. The neurodegeneration cascade events are initiated after the translocation of aggregated polynucleotide within the neuronal cells. The cleaved part of the polynucleotide can cross the neuronal nuclear membrane where the actual phase of polynucleotide disease is triggered, resulting in neuronal death (Jimenez-Sanchez et al. 2017; Illarioshkin et al. 2018).

10.5.1.4 Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive ND characterized by the death of upper motor neurons of the brain and lower motor neurons of the brain stem and spinal cord, leading to paralysis. ALS occurs by the mutation of genes in a motor neuron by environmental factors or by hereditary aspects. There are several gene mutations that have been identified; Cu/Zn superoxide dismutase 1 gene (SOD1), TAR DNA-binding protein 43 (TDP43), fused in sarcoma (FUS)/translocated in sarcoma, and ubiquitin 2 are

some of them. Mutation of the SOD1 gene is the common form in ALS, which was identified in 20% of ALS cases. SOD has three isoforms encoded in the human gene: the cytoplasmic Cu/Zn SOD (SOD1), the mitochondrial Mn SOD (SOD2), and the extracellular Cu/Zn SOD (SOD3). These isoforms are the product of different genes having different cellular localization, but to catalyze some reactions they require metals. During cellular respiration, anionic radical is released in the form of H_2O_2, a toxic reactive oxygen species (ROS), which is further removed by the catalase enzyme to release water and oxygen. Hence, SOD provides antioxidant defense toward the ROS species. The etiopathological events initiated during the progression of ALS follow several mechanisms, which lead to cellular dysfunction. Mutant SOD present in the cytoplasm is also present in mitochondria that alter the normal physiological functions of mitochondria imitating it to release ROS, which triggers apoptosis. Apart from that several cascades of events like neuro-inflammation, glutamate excitotoxicity, protein, and neurofilament aggregations affect the normal function of neuronal cells, leading to degenerations of neuronal cells (Bonafede and Mariotti 2017; Ralli et al. 2019).

10.6 Application of Nanoparticles in ND

Neurodegenerative disease is a chronic condition that still has not got proper treatment because of the drawbacks that are related to the complex structure of the brain and its barrier. Different nanoformulations have extensive physicochemical properties that comply with the natural physiology of the brain and its barrier to boost the penetration rate of therapeutic drugs, which has shown certain improvement in the treatment of disease conditions. Some of them have been elaborated here with their main strategy against the disease condition.

In Alzheimer's disease, plaques get accumulated in the extracellular synaptic gaps of neurocortex region. Clioquinol, chemically derived as 5-chloro-7-iodo-8-hydroxyquinoline, is a quinolone derivative that can dissolve plaques in synaptic gaps. Clioquinol is capable of dissolving plaques in the Alzheimer's disease model of transgenic mice. To treat Alzheimer's disease, nanomaterials can be employed as a carrier to carry clioquinol over the BBB. For example, clioquinol can be encapsulated in n-butyl-cyanoacrylate nanoparticles and delivered over the BBB (Huang et al. 1999; Roney et al. 2005). Donepezil is a cholinesterase inhibitor that is generally unable to penetrate the BBB and is used to treat Alzheimer's disease. Bhavna et al. used PLGA nanoparticles ranging in size from 83.24 nm to 96.10 nm as a nanocarrier to deliver donepezil to the brain. Their findings showed that the nanoparticles were successfully administered into the brain with burst release at first, followed by steady release (Bhavna et al. 2014).

Several novel nanoapproaches have been employed in targeting the brain for the treatment of ND; the method of nanoparticles with ligand conjugated on their surface is one of them. Hernando et al. studied the efficiency of an encapsulated glial cell-derived neurotrophic factor, employing a transactivator of transcription peptide

coupled to a lipid carrier. Wen et al. conjugated odorranalectin to PLGA nanoparticles to increase the transport across the nasal route. In each of these investigations, the intranasal route was utilized to bypass BBB (Hernando et al. 2018; Wen et al. 2011).

Lactoferrin (Lf) is a protein substance that belongs to the transferrin family. It is one of the iron-binding proteins of molecular weight 80 kDa. Lf receptors are extensively expressed on epithelial cells of the respiratory tract and endothelial cells of BBB and neurons. In neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis, these LfR are overexpressed in capillaries and neurons of the brain. Bi et al. used an intranasal method to deliver lactoferrin-modified PEG-PLGA nanoparticles of rotigotine to the target brain for the treatment of Parkinson's disease (Bi et al. 2016).

Carbon nanotubes have been identified as a promising therapeutic strategy in the treatment of PD, AD, and other neurodegenerative diseases where it has been used as a wireless biosensor. Carbon nanotubes placed in a carbon nanochip can track changes in dopamine levels and maintain them at a constant level (Dugan et al. 2001).

Free radicals are produced in the neuronal cells of brain inducing oxidation, and it remains in the brain due to low antioxidant activity; this results in the death of neurons. In ND-like HD, the lack of antioxidant activity in the brain can lead to neuronal damage that significantly leads to its death. As a result, antioxidants can be employed as treatments in Huntington's disease to prevent oxidative stress. Fullerenols are hydrophilic compounds derived from fullerenes that can take free radicals from the exposed environment of the cell. Even fullerenols are referred to as radical sponges because of their capability of removing free radicals. Because of their effective antioxidant properties and hollow spherical shapes, they have been used as carriers in the treatment of HD (Grebowski et al. 2013) Fullerenols' antioxidant properties have been repeatedly established. According to Jin et al., fullerenols were found to be effective in inhibiting glutamate receptors in an antagonistic manner and can thus be employed for neuroprotective purposes (Jin et al. 2000).

References

Akbarzadeh, A. et al. (2013) Liposome: classification , preparation , and applications, pp. 1–9

Bailey RE, Smith AM, Nie S (2004) Quantum dots in biology and medicine. Physica E 25(1):1–12. https://doi.org/10.1016/j.physe.2004.07.013

Barron AR, Khan MR (2008) Carbon nanotubes: opportunities and challenges. Adv Mater Process 166(10):41–43

Bhatia S (2016) Natural polymer drug delivery systems: nanoparticles, plants, and algae. Nat Polym Drug Deliv Syst: Nanoparticles Plant Algae. https://doi.org/10.1007/978-3-319-41129-3

Bhavna B et al (2014) Preparation, characterization, in vivo biodistribution and pharmacokinetic studies of donepezil-loaded PLGA nanoparticles for brain targeting. Drug Dev Ind Pharm 40 (2):278–287. https://doi.org/10.3109/03639045.2012.758130

Bi CC et al (2016) Intranasal delivery of rotigotine to the brain with lactoferrin-modified PEG-PLGA nanoparticles for Parkinson's disease treatment. Int J Nanomedicine 11:6547–6559. https://doi.org/10.2147/IJN.S120939

Bonafede R, Mariotti R (2017) ALS pathogenesis and therapeutic approaches: the role of mesenchymal stem cells and extracellular vesicles. Front Cell Neurosci 11(March):1–16. https://doi.org/10.3389/fncel.2017.00080

Cano A et al (2020) Current advances in the development of novel polymeric nanoparticles for the treatment of neurodegenerative diseases. Nanomedicine 15(12):1239–1261. https://doi.org/10.2217/nnm-2019-0443

Cascione M et al (2020) The new Frontiers in neurodegenerative diseases treatment: liposomal-based strategies. Front Bioeng Biotechnol 8. https://doi.org/10.3389/fbioe.2020.566767

Dugan LL et al (2001) Fullerene-based antioxidants and neurodegenerative disorders. Parkinsonism Rel Disord 7(3):243–246. https://doi.org/10.1016/S1353-8020(00)00064-X

El-Say KM, El-Sawy HS (2017) Polymeric nanoparticles: promising platform for drug delivery. Int J Pharm 528(1–2):675–691. https://doi.org/10.1016/j.ijpharm.2017.06.052

Grebowski J, Kazmierska P, Krokosz A (2013) Fullerenols as a new therapeutic approach in nanomedicine. BioMed Res Int 2013. https://doi.org/10.1155/2013/751913

Guterres SS, Alves MP, Pohlmann AR (2007) Polymeric nanoparticles, Nanospheres and Nanocapsules, for cutaneous applications. Drug Target Insights 2:117739280700200. https://doi.org/10.1177/117739280700200002

Hernando S et al (2018) Intranasal administration of TAT-conjugated lipid nanocarriers loading GDNF for Parkinson's disease. Mol Neurobiol 55(1):145–155. https://doi.org/10.1007/s12035-017-0728-7

Huang X et al (1999) The Aβ peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. Biochemistry 38(24):7609–7616. https://doi.org/10.1021/bi990438f

Iga AM et al (2007) Clinical potential of quantum dots. J Biomed Biotechnol 2007. https://doi.org/10.1155/2007/76087

Illarioshkin SN et al (2018) Molecular pathogenesis in Huntington's disease. Biochem Mosc 83 (9):1030–1039. https://doi.org/10.1134/S0006297918090043

Jimenez-Sanchez M et al (2017) Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. Cold Spring Harb Perspect Med 7(7):1–22. https://doi.org/10.1101/cshperspect.a024240

Jin H et al (2000) Polyhydroxylated C60, fullerenols, as glutamate receptor antagonists and neuroprotective agents. J Neurosci Res 62(4):600–607. https://doi.org/10.1002/1097-4547(20001115)62:4<600::AID-JNR15>3.0.CO;2-F

Kumar A, Singh A, Ekavali (2015) A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep 67(2):195–203. https://doi.org/10.1016/j.pharep.2014.09.004

Kumar A et al (2020a) Nanotheranostic applications for detection and targeting neurodegenerative diseases. Front Neurosci 14:1–11. https://doi.org/10.3389/fnins.2020.00305

Kumar B et al (2020b) Liposomes: novel drug delivery approach for targeting Parkinson's disease. Curr Pharm Des 26(37):4721–4737. https://doi.org/10.2174/1381612826666200128145124

Modi G, Pillay V, Choonara YE (2010) Advances in the treatment of neurodegenerative disorders employing nanotechnology. Ann N Y Acad Sci 1184:154–172. https://doi.org/10.1111/j.1749-6632.2009.05108.x

Orive G et al (2003) Drug delivery in biotechnology: present and future. Curr Opin Biotechnol 14 (6):659–664. https://doi.org/10.1016/j.copbio.2003.10.007

Pal SL et al (2011) Nanoparticle: an overview of preparation and characterization. J Appl Pharm Sci 1(6):228–234

Parveen S, Misra R, Sahoo SK (2012) Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine 8(2):147–166. https://doi.org/10.1016/j.nano.2011.05.016

Ralli M et al (2019) Amyotrophic lateral sclerosis: autoimmune pathogenic mechanisms, clinical features, and therapeutic perspectives. Israel Med Assoc J 21(7):438–443

Reilly RM (2007) Carbon nanotubes: potential benefits and risks of nanotechnology in nuclear medicine. J Nucl Med 48(7):1039–1042. https://doi.org/10.2967/jnumed.107.041723

Roney C et al (2005) Targeted nanoparticles for drug delivery through the blood-brain barrier for Alzheimer's disease. J Control Rel 108(2–3):193–214. https://doi.org/10.1016/j.jconrel.2005.07.024

Singh E, Devasahayam G (2020) Neurodegeneration by oxidative stress: a review on prospective use of small molecules for neuroprotection. Mol Biol Rep 47(4):3133–3140. https://doi.org/10.1007/s11033-020-05354-1

Spuch C, Navarro C (2011) Liposomes for targeted delivery of active agents against neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). J Drug Deliv 2011:1–12. https://doi.org/10.1155/2011/469679

Tiwari G et al (2012) Drug delivery systems: an updated review. Int J Pharm Invest 2(1):2. https://doi.org/10.4103/2230-973x.96920

Wen Z et al (2011) Odorranalectin-conjugated nanoparticles: preparation, brain delivery and pharmacodynamic study on Parkinson's disease following intranasal administration. J Control Rel 151(2):131–138. https://doi.org/10.1016/j.jconrel.2011.02.022

Xu W, Ling P, Zhang T (2013) Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. J Drug Deliv 2013(1):1–15. https://doi.org/10.1155/2013/340315