Nanoparticle Drug Delivery System for the Treatment of Neurological Disorder

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Abstract

It is challenging to directly target neurological illnesses because of the complexity of the central nervous system, which is difficult to get around the brain's built-in defense mechanisms. The development of nanotechnology offers promising possibilities for overcoming this issue. Nano-engineered molecules can be made to pass the blood-brain barrier, target certain cells or signaling systems, react to endogenous cues, operate as vehicles for delivering genes, or act as a matrix to encourage axon extension and sustain cell survival. Nanotechnology is an emerging, interdisciplinary field of science and engineering with the potential to significantly alter how we manage and control materials and devices at the molecular level (often defined within the range of 1–100 nm), using physical or chemical approaches. We review existing regeneration treatments for neurological disorders, as well as nanotechnology's role as a nano-carrier and the technical, manufacturing, and regulatory difficulties that occur from the conception of nanoparticle-based regenerative treatments through their formulation. Additionally, it has been addressed what the objectives and targeted tactics for the various types of brain pathology are.

Keywords: Neurological disorder, Nanoparticle, Blood brain barrier, Central nervous system.
DOI Number: 10.14704/nq.2022.20.9.NQ44736 **Neuro Quantology 2022; 20(9):6279-6284**

1. Introduction

Biomedical and pharmaceutical researchers have worked to successfully combine various treatment modalities in order to develop new and more effective therapeutics to treat diseases affecting the central nervous system. Nanotechnology has been used for decades to overcome the limitations of current pharmacotherapy for neurological disorders. Various medications are used to treat it, but there is yet no cure. The blood-brain barrier effectively protects the brain, and because many conventional drugs cannot cross it in effective doses less than 1% of all drugs reach the central nervous system. Many central nervous system diseases, including stroke, neurodegenerative diseases, and brain tumors, go untreated. Targeting medications to the brain is therefore one of the trickiest problems [Spandana et al., 2020]. Using drug delivery systems composed of nanoparticles to encapsulate active molecules is a smart way to get around some of the drawbacks of traditional drugs. It is the technology that is used to create materials, tools, and electric biosensors with sizes ranging from a few to a few hundred nanometers, and it is capable of delivering drugs into difficult places like the brain, while also protecting therapeutic agents and effectively delivering them to the targeted sites. Furthermore, nano-carriers have the ability to transport drugs, oligonucleotides, contrast agents, and genes to a target site in the central nervous system with minimal or no systemic side effects and no blood brain barrier harm. Nanoparticles are helpful tools for visualising the human body or organs. In light of these factors, the suitability of nano-carrier-based drug delivery systems for precise brain dosage is now being investigated [Spandana et al., 2020]. Nowadays, it is suggested to be the potential development of nanoparticle loaded drug for neurological disorder. The majority of neurological disorders, including brain tumours, degenerative Alzheimer's disease, Parkinson's disease, and others with an inflammatory component, are becoming more common and

have unknown causes. Potential innovative and minimally invasive techniques for the treatment and diagnostics of various neurological illnesses include nanodelivery technologies. They have also demonstrated great promise in providing therapeutic and diagnostic help after systemic delivery. We examine the most recent developments in current knowledge of a number of prevalent neurological illnesses, particularly the use of nanoparticles in their treatment and detection [Sim et al., 2020]. The complex neurological illnesses impact around 1.5 billion people worldwide, and the number is frighteningly rising as a result of poor treatment. No conventional formulation has been able to demonstrate a hopeful impact on the management or prevention of neurodegeneration till date. Nano delivery methods, on the other hand, have demonstrated deeper effect and improved brain area penetration. The advancement of nanotechnology in recent decades has opened up new possibilities for targeted therapeutic delivery and contributed to the creation of nano-based drug delivery systems. These nano-based medication delivery systems deliver anti-neurological medications to the target site at high concentrations while preventing the accumulation of these drugs in healthy organs [Guo and Li, 2022].

2. Mechanism of nanoparticle drug delivery system in neurological disorder

A significant barrier to drugs reaching the CNS is the blood brain barrier. Because of the brain's exceptional vascularization, each neuron can interact with a capillary. Targeting pharmaceuticals to the brain is one of the most difficult problems because the blood brain barrier is unable to deliver the drug into the brain. The blood brain barrier has restrictions that have been overcome using a variety of invasive and non-invasive techniques. Only tiny, lipophilic substances can pass through the blood brain barrier with ease. Additional active transport mechanisms, including as receptor-mediated transport and carrier-mediated transport, are needed for larger molecules. When designing a drug that will enter the central nervous system through systemic circulation, several transport systems must be taken into account. Henceforth, nanoparticle is one of the promising methods for a successful drug delivery to the central nervous system with improved drug efficacy and reduced systemic drug toxicity [Spandana et al., 2020]. There are different types of nanoparticles available for the treatment of neurological disorder. These are metallic nanoparticle, radio-labelled nanoparticle, quantum dots nanoparticle, liposome nanoparticle, carbon tubes nanoparticle, magnetic nanoparticle, and dendrimer [Figure 1]. Receptor-mediated transcytosis, adsorption-mediated transcytosis, and paracellular transport are the principal routes that enable blood brain barrier penetration (stem cells and immune cells, macrophages, and monocytes) [Figure 2]. In addition, a variety of nanoscale materials, including organic, inorganic, polymeric, and carbon-based substances as well as extracellular vesicles, liposomes, red blood cell membranes, and metal nanostructures, have been used to construct nanomedicines. These nanoparticles significantly enhance the pharmacokinetics and biodistribution of medicines within the central nervous system [Hanif et al., 2020].

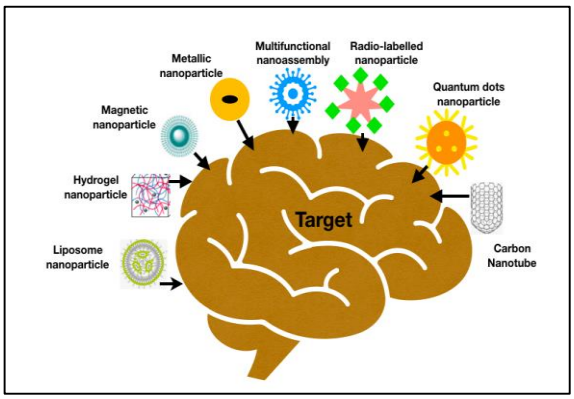

Figure 1. Types of nanoparticles involved in targeting brain disorder

Like, quantum dots (QDs) have the ability to pass across the blood brain barrier and migrate into the brain with blood flow. Although QDs have the ability to produce fluorescent light and can therefore be used to deliver drugs, the interactions between QDs and the cells and tissues of the nervous system are not yet fully understood [Liu et al., 2006]. Liposomes are small, spherical vesicles that include a hydrophilic compartment in the centre that is surrounded by one or more phospholipid bilayers, giving them physical similarities to cell membranes. They are employed as a tactical method for delivering drugs, proteins, and

peptides. The research demonstrated the usage of liposomes as an anti-Alzheimer drug. While in case of dendrimers, due to its various characteristics including excellent water solubility, biocompatibility, polyvalency, and exact molecular weight, dendrimers have received more attention than traditional polymers. This makes them suitable for targeted drug administration in the brain [Naqvi et al., 2020]. Other nanoparticle like magnetic nanoparticle, multifunctional nanoassemblies, and radio-labelled nanoparticle have shown great potential as an advanced treatment of neurological disorder [Correia et al., 2022].

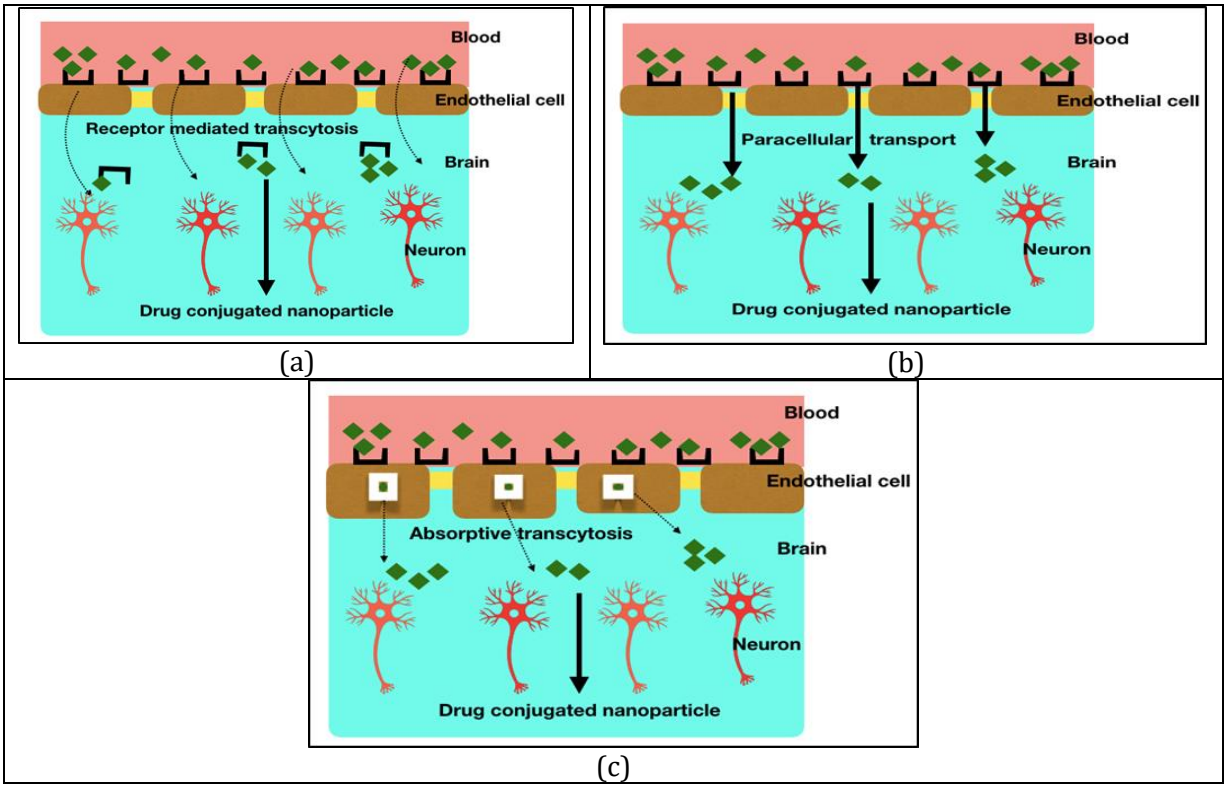

Figure 2: Mechanism of nanoparticle drug delivery system in neurological disorder through, (a) receptor mediated transcytosis; (b) paracellular transport; (c) absorptive transcytosis

3. Application of Nanotechnology in neurological disorder

Nanoparticles are the tiniest particles, often falling between 1 and 100 nm in size and rarely reaching 1,000 nm. The metals or compounds are altered, either naturally or artificially, to generate the particles. With varied physical and chemical properties, various types of nanoparticles, including metal and metal oxides, liposomal, polymeric, fullerenes, nanoemulsions, solid-lipid (SL), polylactide-co-glycoside (PLGA) NPs, and others, have been created thus far [Ngowi et al., 2021]. The uses of nanotechnology in different neurological disease is explained as below:

3.1. Alzheimer disease

Alzheimer's disease (AD) frequently has an impact on thought, memory, and behaviour. According to reports, the brain changes started roughly 10 to 20 years before AD symptoms and a diagnosis were made. It is a typical form of dementia characterised by age-related, progressive neuronal degeneration leading to decreased cognitive function and other neuropathological characteristics. The greatest obstacle to treating and diagnosing this fatal disease at an early stage is the lack of reliable biomarkers [Leszek et al., 2017]. One of the pathogenic characteristics linked to the development of neurodegenerative illnesses, including AD, is the build up of Tau proteins. According to a recent study, IO NPs and protein-capped cadmium sulphide may both efficiently prevent Tau proteins from polymerizing and fibrillizing, with inhibition rates of 63 and 49%, respectively. Additionally, it has been demonstrated that surface-coated Au NPs can lessen aggregation. Au NPs have also been shown to induce cytoprotective benefits in an AD

rat model by enhancing antioxidant status and anti-inflammatory responses [Ngowi et al., 2021].

Research Gap: The only hurdle between the treatments of AD with nanotechnology is lack of reliable biomarker which in not yet fully understood.

3.2. Parkinson Diseases

The understanding of the pathogenesis of Parkinson's disease has benefited greatly from nanotechnology. Early neuronal loss can be imaged using nanoparticles, and amyloid peptides in cerebrospinal fluid can be found and measured using nanodevices. In experimental models of Parkinson's disease, the administration of antiparkinsonian drugs, neurotrophic factors, antioxidants, neuroprotective, and antiapoptotic agents has been explored using nanomaterials. This illness can be recognised by the decline in motor abilities brought on by the death of dopamine-releasing neurons [Sharma et al., 2021]. Given the wide range of nanomaterials that offer advantageous properties for theranostic drug delivery techniques, nanoparticle-based technology is positioned as a leading approach for treating disease among the different possibilities. Dopamine-loaded nanoparticle formulation has been investigated to alter therapy bioavailability, effectiveness, and stability. To encase dopamine, a variety of nanomaterials have been created, including liposomes, chitosan nanoparticles, quantum rods, cellulose acetate phthalate, borneol and lactoferrin co-modified nanoparticles, and solid lipid nanoparticles. However, to the best of our knowledge, no studies have been finished for the treatment of Parkinson's diseases at the clinical level. Some of these nanomaterial-based technologies have already been tried in pre-clinical Parkinson's diseases models [Monge-Fuentes et al., 2021].

Research Gap: Lack of clinical evidences with reference of application of nano-formulation drugs in Parkinson's disease.

3.3. Multiple sclerosis

A complex illness with numerous pathogenic mechanisms and pathways is called as multiple sclerosis. Early accurate diagnosis and specific treatment regimens based on a multifunctional nanotechnology approach are necessary for successful multiple Sclerosis management and medical care. According to recent study from Northwestern Medicine, a biodegradable nanoparticle proves to be the ideal carrier for covertly delivering an antigen that deceives the immune system into ending its attack on myelin and stops a mouse model of relapsing remitting multiple sclerosis [Singh et al., 2012]. The use of nanotechnologies is resulting in the development of completely new methods and treatments for the precise delivery of drugs to different tissues. A new study headed by experts at the University of California, Irvine found that a bone marrow stem cell-derived nanotechnology therapy could potentially be utilised to treat people with multiple sclerosis [Riazifar et al., 2019]. In addition to demyelination, another study shows that neuroinflammation is a feature of multiple sclerosis, and data from animal models points to the interaction of T cells, astrocytes, and microglia. Targeting neuroinflammation as an effective treatment method has showed promise in multiple sclerosis in its advanced phases. Drug diffusion over the blood brain barrier and the multiple sclerosis brain's neurovasculature, however, continues to be a significant obstacle [Singh et al., 2012].

Research Gap: Lack of established biomarker to target via nanotechnology.

3.4. Epilepsy

A significant neurological condition called epilepsy affects 1% of Indians. It is difficult for scientists to find non-invasive treatments for epilepsy. For the treatment of epilepsy, many nose-to-brain dosage-forms have been investigated. For patients with epilepsy, theranostic solutions like implanted gadgets and biodegradable nanomaterials provide better, more individualised ways to diagnose and treat them. Site-specific delivery made possible by combining nanotechnology with a nose-to-brain method can aid in improving therapeutic effectiveness. Additionally, it will reduce the negative effects and patient noncompliance seen with traditional administration methods. Delivery of peptides may be a novel method for managing epilepsy. Drug-loaded intranasal nano-formulations have a variety of possible uses for treating epilepsy [Shringarpure et al., 2021]. Carbamazepine was recently successfully encapsulated in polymeric nanoparticles by the

authors. These nanoparticles showed that carbamazepine in capsule form was 30 times more efficacious against seizures than carbamazepine in free form. Additionally, they showed how the P-glycoprotein-mediated drug resistance caused by carbamazepine encapsulation into polymeric nanoparticles could be overcome. Solid-lipid nanoparticles have been used in numerous trials to treat epilepsy. The biodistribution of solid lipid nanoparticles loaded with alprazolam was studied by the authors. In comparison to the alprazolam solution, they found that solid lipid nanoparticles loaded with encapsulated alprazolam had a greater targeting efficiency [Bonilla et al., 2022].

Research Gap: Lack of established clinical study

3.5. Stroke

One of the main global causes of mortality and morbidity is stroke. By 2030, it is anticipated that there would be 23 million new cases of stroke and 7.8 million deaths related to them. The underlying pathophysiology's main contributor is still thromboembolism. Therapy must concentrate on regulating and reducing the series of apoptotic events that lead to neuronal cell death due to the complexity of the molecular mechanisms and their physiological effects. More specifically, nanoparticles can be designed to release their payload in response to the various extracellular processes that are present around the clot and in the ischemic penumbra during a stroke. They can also be used to help detect pathological hallmarks that are present at different stages of the stroke's progression [Sarmah et al., 2017]. One of the main objectives of stroke research is high resolution imaging of the cerebral vascular. This is becoming more feasible due to adaptations of current approaches by nanotechnology. One of the most popular methods for diagnosing stroke is computerised tomography based on X-rays, which enables the differentiation between ischemic and hemorrhagic stroke as well as the identification of areas with different levels of cerebral perfusion [Landowski et al., 2020]. However, there are still a number of challenges in the field of treating neurological illnesses like stroke. The blood brain barrier, a constrictive and crucial part of defending the brain from any dangerous compounds circulating in the blood and of blocking the admission of small molecules and, for the most part, all macromolecules, is by far the biggest obstacle.

Research Gap: Lack of evidences to overcome the obstacles during treatment with nanoparticle in blood brain barrier.

4. Conclusion

Research on alternative therapies for treating neurological disorders has been directed toward nanotechnology due to the growing morbidity and mortality risk associated with neurological disorders worldwide, the risks and inadequacies of the current therapies, and the need for more effective and secure treatments. It might be difficult to find therapies for neurological disorders. This is partly due to the complexity of brain biology and the rapid evolution of diseases. Further complicating the issue are the challenges presented by researching the biology of an organ that interacts with every other organ in the body and is protected by a substantial bone skull. This technology method has promise for the treatment and diagnosis of disease. Using polymer-based approaches and nanomaterials, several nano solutions aimed at better drug administration to patients with near diseases are being researched. Expertise in biomedical sciences (neuroscience, immunology, pharmacology, molecular imaging), materials science, biomaterials, and pharmaceuticals (polymers, nanomaterials, drugs, and genetics) is required to create and speed up the treatment of disorders connected to the brain. Furthermore, we concluded every section with a research gap hoping that this discussed research gap will fulfil in further research investigation.

Acknowledgements

The authors are thankful to the Head, Department of Chemistry, University college of Science, OU for providing laboratory facilities. One of the authors M. Kavitha is thankful to UGC-New Delhi, India for financial support in the form of Start-up grant. PMR is grateful to TSCOST-under Project Related Grants (File No. No. 03/TSCOST/DST-PRG/2021-22, DT.31-12-2021) for financial support.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Spandana, K. A., Bhaskaran, M., Karri, V. R., & Natarajan, J. (2020). A comprehensive review of nano drug delivery system in the treatment of CNS disorders. *Journal of Drug Delivery Science and Technology*, *57*, 101628.
2. Sim, T. M., Tarini, D., Dheen, S. T., Bay, B. H., & Srinivasan, D. K. (2020). Nanoparticle-based technology approaches to the management of neurological disorders. *International Journal of Molecular Sciences*, *21*(17), 6070.
3. Guo, Y., & Li, P. (2022). Recent highlights in periopeative neurological disorders, from bench to bedside. *CNS Neuroscience & Therapeutics*, *28*(4), 467-469.
4. Hanif, S., Muhammad, P., Chesworth, R., Rehman, F. U., Qian, R. J., Zheng, M., & Shi, B. Y. (2020). Nanomedicine-based immunotherapy for central nervous system disorders. *Acta Pharmacologica Sinica*, *41*(7), 936-953.
5. Liu, G., Men, P., Harris, P. L., Rolston, R. K., Perry, G., & Smith, M. A. (2006). Nanoparticle iron chelators: a new therapeutic approach in Alzheimer disease and other neurologic disorders associated with trace metal imbalance. *Neuroscience letters*, *406*(3), 189-193.
6. Naqvi, S., Panghal, A., & Flora, S. J. S. (2020). Nanotechnology: a promising approach for delivery of neuroprotective drugs. *Frontiers in neuroscience*, *14*, 494.
7. Correia, A. C., Monteiro, A. R., Silva, R., Moreira, J. N., Lobo, J. S., & Silva, A. C. (2022). Lipid nanoparticles strategies to modify pharmacokinetics of central nervous system targeting drugs: crossing or circumventing the blood-brain barrier (BBB) to manage neurological disorders. *Advanced Drug Delivery Reviews*, 114485.
8. Ngowi, E. E., Wang, Y. Z., Qian, L., Helmy, Y. A. S. H., Anyomi, B., Li, T., ... & Ji, X. Y. (2021). The application of nanotechnology for the diagnosis and treatment of brain diseases and disorders. *Frontiers in Bioengineering and Biotechnology*, *9*, 629832.
9. Leszek, J., Md Ashraf, G., Tse, W. H., Zhang, J., Gasiorowski, K., Fidel Avila-Rodriguez, M., ... & Aliev, G. (2017). Nanotechnology for Alzheimer disease. *Current Alzheimer Research*, *14*(11), 1182-1189.
10. Sharma, S., Rabbani, S. A., Agarwal, T., Baboota, S., Pottoo, F. H., & Kadian, R. (2021). Nanotechnology driven approaches for the management of Parkinson's disease: Current status and future perspectives. *Current Drug Metabolism*, *22*(4), 287-298.
11. Monge-Fuentes, V., Biolchi Mayer, A., Lima, M. R., Geraldes, L. R., Zanotto, L. N., Moreira, K. G., ... & Mortari, M. R. (2021). Dopamine-loaded nanoparticle systems circumvent the blood–brain barrier restoring motor function in mouse model for Parkinson's Disease. *Scientific Reports*, *11*(1), 1-16.
12. Singh, A. V., Khare, M., Gade, W. N., & Zamboni, P. (2012). Theranostic implications of nanotechnology in multiple sclerosis: a future perspective. *Autoimmune diseases*, *2012*.
13. Riazifar, M., Mohammadi, M. R., Pone, E. J., Yeri, A., Lasser, C., Segaliny, A. I., ... & Zhao, W. (2019). Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders. *ACS nano*, *13*(6), 6670-6688.
14. Shringarpure, M., Gharat, S., Momin, M., & Omri, A. (2021). Management of epileptic disorders using nanotechnology-based strategies for nose-to-brain drug delivery. *Expert Opinion on Drug Delivery*, *18*(2), 169-185.
15. Bonilla, L., Esteruelas, G., Ettcheto, M., Espina, M., García, M. L., Camins, A., ... & Sánchez-López, E. (2022). Biodegradable nanoparticles for the treatment of epilepsy: From current advances to future challenges. *Epilepsia Open*, *7*, S121-S132.
16. Sarmah, D., Saraf, J., Kaur, H., Pravalika, K., Tekade, R. K., Borah, A., ... & Bhattacharya, P. (2017). Stroke management: An emerging role of nanotechnology. *Micromachines*, *8*(9), 262.
17. Landowski, L. M., Niego, B. E., Sutherland, B. A., Hagemeyer, C. E., & Howells, D. W. (2020, July). Applications of nanotechnology in the diagnosis and therapy of stroke. In *Seminars in Thrombosis and Hemostasis* (Vol. 46, No. 05, pp. 592-605). Thieme Medical Publishers.