Chapter 5

Nanoparticle-Based Drug Delivery Strategies for Crossing the Blood-Brain Barrier in Alzheimer 's disease

Monika.K[a], Nagammal.B[a], A.Ramya[b*]

[a]*B.Pharm Student, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

[b*]*Assistant Professor, Department of Pharmacology, School of Pharamaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

** Corresponding Author:ramaya.sps@vistas.ac.in*

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by progressive loss of neuronal function, memory impairment, and cognitive decline. Due to the aging population, it is the most prevalent cause of dementia globally and a significant public health concern. Alzheimer's disease is characterized by intracellular neurofibrillary tangles made of hyperphosphorylated tau protein, extracellular amyloid-beta plaque deposition, and persistent neuroinflammation. The brain's gradual neuronal degeneration and disruption of synaptic transmission are caused by these pathological alterations [1][3].The blood–brain barrier (BBB), a highly selective biological barrier that shields the brain from dangerous substances flowing in the bloodstream, is one of the main obstacles to treating Alzheimer's disease. The BBB restricts the delivery of therapeutic medicines to the central nervous system even though it is essential for preserving brain homeostasis. Poor therapy outcomes for neurological illnesses are caused by many conventional medications' inability to effectively pass the blood-brain barrier [3][4].Recent developments in nanotechnology have presented medication delivery methods based on nanoparticles as viable ways to get around these limitations. Drug stability, bioavailability, and targeted delivery to certain brain regions impacted by neurodegeneration can all be improved by nanoparticles. The potential of a variety of nanocarriers, including lipid nanoparticles, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, to carry therapeutic drugs across the blood-brain barrier via processes such receptor-mediated and adsorptive-mediated transcytosis has been studied [2][5][6].The pathophysiology of Alzheimer's disease, difficulties in delivering medications to the brain, and new advancements in therapeutic approaches based on nanoparticles are all covered in this chapter.

Keywords: Alzheimer’s disease, Blood–Brain Barrier (BBB), Nanoparticle-based drug delivery, Brain targeting, Neurodegenerative diseases.

1. Introcution

The majority of dementia cases globally are caused by Alzheimer's disease, the most common neurodegenerative illness. Progressive decline in cognitive abilities, such as memory, reasoning capacity, and language proficiency, is a hallmark of the illness. Patients' everyday functioning and quality of life are severely hampered by severe behavioral and psychiatric symptoms as the illness progresses. Alzheimer's disease is becoming more common, which puts a heavy strain on healthcare systems and highlights the need for efficient therapeutic measures [3][5]. Alzheimer's disease is caused by a number of interrelated biological processes. Extracellular

ISBN 978-816855388-0

plaques that obstruct neuronal communication are created when amyloid-beta peptides build up in the brain. Furthermore, aberrant tau protein phosphorylation causes neurofibrillary tangles to form inside neurones, impairing intracellular transport and accelerating neuronal deterioration. Oxidative stress, mitochondrial malfunction, and persistent neuroinflammatory reactions accompany these pathogenic alterations and hasten neuronal destruction [1][3] .

2. Blood-brain barrier and drug delivery challenges

The exchange of chemicals between the bloodstream and the central nervous system is controlled by the blood–brain barrier, a sophisticated and highly specialised biological system. Large or hydrophilic molecules cannot passively diffuse into the brain because it is made up of closely spaced endothelial cells that create continuous tight connections. The endothelial cells are surrounded by astrocytes and pericytes, which offer extra structural and functional support to preserve the integrity of the blood-brain barrier [3][4]. The BBB poses a serious obstacle to medication delivery even if it shields the brain from poisons and infections. Many therapeutic treatments are unable to successfully cross the blood-brain barrier, especially big macromolecules and hydrophilic chemicals. Because of this, only a tiny portion of medications are able to reach the brain, which reduces their therapeutic efficacy for treating neurological conditions like Alzheimer's disease [3][7]. The BBB has a number of efflux transporters, such as P-glycoprotein and multidrug resistance proteins, in addition to tight junctions. These transporters actively remove foreign substances from endothelial cells and return them to the bloodstream. Drug buildup in brain tissues is further restricted by these processes. Research in the creation of sophisticated medication delivery methods is now primarily focused on overcoming these obstacles [4][6]. Drug delivery systems based on nanoparticles have shown promise as a means of circumventing or taking advantage of BBB transport processes. Nanoparticles can interact with cellular transport channels and help deliver therapeutic drugs into the brain because of their small size and adaptable surface characteristics [2][6].

3. Nanopartical-based drug delivery systems

By making it possible to create nanoscale carriers that can carry therapeutic drugs to precise target locations, nanotechnology has completely transformed the field of medication delivery. Usually ranging in size from 1 to 100 nanometres, nanoparticles have special physicochemical characteristics that enable them to effectively interact with biological systems. When compared to traditional drug delivery methods, these systems have a number of benefits, including as increased solubility, regulated drug release, and improved drug stability [2][6]. Protecting medications from enzymatic degradation and early removal from the body is one of the main benefits of drug delivery systems based on nanoparticles. When medications are encapsulated in nanoparticles, their bioavailability and circulation time both increase. Moreover, nanoparticles can be designed with surface alterations that enable them to identify and attach to particular BBB receptors, enabling tailored transit into brain regions [1][5]. Dendrimers, inorganic nanocarriers, polymeric nanoparticles, and lipid-based nanoparticles have all been studied as potential treatments for Alzheimer's disease. By delivering therapeutic drugs specifically to damaged brain areas, these nanosystems can increase treatment efficacy while reducing systemic negative effects [5,6]

ISBN 978-816855388-0

4. Types of nanoparticles used for brain drug delivery

The potential of several nanoparticle forms to enhance drug transport across the blood-brain barrier in the treatment of Alzheimer's disease has been studied. Due to their great biocompatibility and capacity to incorporate both hydrophilic and hydrophobic medications, lipid-based nanoparticles are the most extensively researched of them. Because their lipid structure is similar to biological membranes, liposomes and solid lipid nanoparticles are very helpful in facilitating drug transport into brain regions and improving their interaction with cellular membranes. Lipid nanoparticles can also enhance the pharmacokinetic characteristics of medicinal compounds and shield them from enzymatic breakdown [5]. Another significant class of nanocarriers for targeted brain medication delivery is polymeric nanoparticles. Biodegradable polymers including chitosan, polyethylene glycol, and polylactic-co-glycolic acid (PLGA) are frequently used to create these nanoparticles. Because polymeric nanoparticles offer sustained and regulated drug release, therapeutic medicines can be active in the body for extended periods of time.

Moreover, ligands or antibodies that selectively attach to blood-brain barrier receptors can be added to their surfaces to improve targeted delivery to impacted brain regions [1][5]. Apart from lipid and polymeric nanoparticles, other nanosystems have also been investigated, including dendrimers, gold nanoparticles, and silica-based nanoparticles. Drug attachment and targeting can be facilitated by the highly branching structure of dendrimers, which have several functional groups. Due to their distinct optical and physicochemical characteristics, metallic nanoparticles—especially gold nanoparticles—are beneficial for both drug administration and diagnostic imaging applications. In neurodegenerative illnesses, these various nanoparticle systems present intriguing methods for enhancing therapeutic delivery to the brain[5][6] .

5. Mechanisms of nanopartical transport across the BBB

Several biological transport pathways allow nanoparticles to get through the blood-brain barrier. Receptor-mediated transcytosis is one of the key processes. This method involves functionalising nanoparticles with ligands that attach to particular receptors on the blood–brain barrier's endothelial cells. These receptors include low-density lipoprotein receptors, insulin receptors, and transferrin receptors. Following its binding to these receptors, the nanoparticle is taken up by the endothelial cell and moved into brain tissues through the blood-brain barrier[6]. Adsorptive-mediated transcytosis is another significant mechanism that happens when negatively charged cell membranes and positively charged nanoparticles interact electrostatically. These interactions let nanoparticles pass through the barrier and are more likely to be absorbed by endothelial cells. This process can improve the penetration of nanoparticles into the brain, but it is less selective than receptor-mediated transport[6]. PEGylation, ligand conjugation, and antibody attachment are examples of surface modification methods that enhance nanoparticles' capacity to pass the blood-brain barrier. These changes improve the stability of nanoparticles, extend their stay in circulation, and improve their capacity to target damaged brain regions. Consequently, nanoparticle transport across the blood-brain barrier has emerged as a key tactic in the creation of sophisticated drug delivery systems for Alzheimer's [1][6] .

ISBN 978-816855388-0

6. Recent advances in nanopartical brain delivery

Advanced nanoparticle systems specifically intended for the targeted treatment of neurodegenerative illnesses have been developed as a result of recent nanomedicine research. Researchers have created multipurpose nanoparticles that can transport therapeutic medications straight to the brain's diseased areas. Targeting ligand-containing surface-modified nanoparticles can attach to brain endothelial cell receptors selectively, enabling them to concentrate in Alzheimer's disease-affected brain regions [4][6]. The creation of nanoparticles that can target amyloid-beta plaques, a significant pathogenic aspect of Alzheimer's disease, is another encouraging breakthrough. Drugs can now be administered straight to the sites of pathology thanks to specific nanoparticle formulations that have been designed to identify and attach to these plaques. This focused strategy could halt the development of neurodegeneration and lessen plaque buildup [4][7]. Nanoparticles are being investigated for diagnostic applications in addition to therapeutic delivery. Certain nanoparticles can be employed as imaging agents to identify early pathological alterations in the brain, facilitating an earlier diagnosis and better treatment of the illness. Theranostics, the term for these integrated therapeutic and diagnostic applications, is a new field of study in the management of neurodegenerative diseases [6] .

7. Future perspectives

Before nanoparticle-based drug delivery systems can be widely used in clinical practice, a number of issues need to be resolved, despite the fact that they have shown encouraging outcomes in experimental investigations. The long-term safety and possible toxicity of nanoparticles are two of the main issues. Over time, some nanomaterials may build up in tissues, potentially having negative biological effects. Therefore, prior to clinical application, a thorough assessment of the biocompatibility and toxicity of nanoparticles is required [1][6]. The standardisation and large-scale manufacturing of nanoparticle compositions present another difficulty. Strict quality control procedures and cutting-edge technology are needed to produce nanoparticles with uniform stability, drug loading capacity, and size. Furthermore, the clearance process for innovative treatments may be delayed due to the ongoing evolution of regulatory requirements for nanomedicine products [6]. Future studies should concentrate on creating safer nanomaterials, enhancing targeting effectiveness, and carrying out clinical trials to assess the efficacy of medicines based on nanoparticles in human patients. It is anticipated that developments in biotechnology, materials science, and nanomedicine will aid in the creation of next-generation drug delivery methods that can overcome the present constraints in the treatment of Alzheimer's disease [6][7] .

8. Conclusion

Alzheimer's disease is still one of the most difficult neurodegenerative conditions because of its complicated aetiology and few available treatments. The blood-brain barrier, which limits the transport of many therapeutic drugs to brain tissues, is one of the main challenges in creating effective medicines. The therapeutic efficacy of conventional drug delivery methods is typically diminished by their inability to attain sufficient drug concentrations in the brain [1][3]. Drug delivery systems based on nanoparticles offer a potential answer to this problem. Nanoparticles have the potential to greatly enhance Alzheimer's disease treatment outcomes by increasing

ISBN 978-816855388-0

medication stability, boosting bioavailability, and facilitating targeted administration across the blood–brain barrier. Numerous nanocarriers, such as dendrimers, polymeric nanoparticles, and lipid nanoparticles, have shown the capacity to deliver therapeutic medicines into brain regions via a variety of transport modes[5][6]. The design and performance of nanoparticle systems have been further enhanced by recent developments in nanomedicine, allowing for tailored distribution to diseased areas inside the brain. Nanoparticle-based therapeutics are a promising approach for the future treatment of Alzheimer's disease and other neurodegenerative illnesses, but more study is needed to address safety issues and regulatory obstacles [1][3][6].

References:

[1] Kochman, U., Sitka, H., Kuźniar, J. et al. Targeted Nanoparticles for Drug Delivery Across the Blood–Brain Barrier in Early and Late Stages of Alzheimer's Disease: A Review. Mol Neurobiol 63, 75 (2026). https://doi.org/10.1007/s12035-025-05417-z

[2] Raghunath, K. (2026). Nanotechnology-based drug delivery systems for brain targeting: Recent advances and challenges. International Journal of Exploring Emerging Trends in Engineering (IJOEETE), 12(1).

[3] Le H, Vu GTT, Abioye A, Adejare A. Recent Advances in Nanoparticle-Based Drug Delivery Strategies to Cross the Blood-Brain Barrier in Targeted Treatment of Alzheimer's Disease. Pharmaceutics. 2026 Feb 1;18(2):192. doi: 10.3390/pharmaceutics18020192. PMID: 41754934; PMCID: PMC12944235.

[4] Haro-Martínez, E., Muscolino, E., Moral, N. et al. Crossing the blood–brain barrier: nanoparticle-based strategies for neurodegenerative disease therapy. Drug Deliv. and Transl. Res. 16, 797–824 (2026).

[5] Rajkumar M, Tian F, Javed B, Prajapati BG, Deepak P, Girigoswami K, Karmegam N. Smart Biosensing Nanomaterials for Alzheimer's Disease: Advances in Design and Drug Delivery Strategies to

Overcome the Blood-Brain Barrier. Biosensors (Basel). 2026 Jan 21;16(1):66. doi: 10.3390/bios16010066. PMID: 41590318; PMCID: PMC12838666.

[6] Lee, S., Lee, J., & Lee, K. (2026). Translational roadmap of BBB-targeted nanoparticle strategies for neuroregenerative therapy in neurodegenerative diseases. Biomaterials Science.

[7] Le H, Vu GTT, Abioye A, Adejare A. Recent Advances in Nanoparticle-Based Drug Delivery Strategies to Cross the Blood-Brain Barrier in Targeted Treatment of Alzheimer's Disease. Pharmaceutics. 2026 Feb 1;18(2):192. doi: 10.3390/pharmaceutics18020192. PMID: 41754934; PMCID: PMC12944235.

[8] Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L (2016) Nanoparticle-mediated brain drug delivery: overcoming blood–brain barrier to treat neurodegenerative diseases. J Control Release 235:34–47

[9] Habib S, Singh M (2022) Angiopep-2-Modified Nanoparticles for Brain-Directed Delivery of Therapeutics: A Review. Polymers (Basel) 14(4):763.

[10] Teixeira MI, Lopes CM, Amaral MH, Costa PC (2023) Surface-modified lipid nanocarriers for crossing the blood-brain barrier (BBB): a current overview of active targeting in brain diseases. Colloids Surf B Biointerfaces 221:112999.

[11] Banks WA (2011) Drug Delivery to the Brain in Alzheimer's Disease: Consideration of the Blood-brain Barrier. Adv Drug Deliv Rev 64(7):629–639.

ISBN 978-816855388-0