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Review Article

Breaking the Blood-Brain Barrier: Nanoparticle Innovations in Brain Drug Delivery

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Abstract: The blood–brain barrier (BBB), a highly specialized and selective interface, is essential for preserving the homeostasis of the central nervous system (CNS) but also presents a significant barrier to the efficient administration of medications for neurological conditions. The BBB limits the passage of most therapeutic drugs due to its tight junctions, efflux transporters, and regulated permeability. As a result, there are few therapy choices for ailments including brain tumors, Parkinson's disease, Alzheimer's disease, stroke, and other CNS-related disorders. Conventional drug delivery methods, such as altering pharmaceuticals chemically and using intrusive administration. Drug delivery technologies based on nanotechnology have been a viable way to get over BBB-related restrictions in recent years. This paper offers a thorough summary of methods for improving drug transport across the blood-brain barrier that are mediated by nanoparticles. The structural features, BBB penetration mechanisms, and therapeutic applications of a variety of nanocarrier systems—including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, dendrimers, inorganic nanoparticles, and biomimetic carriers like exosomes—are examined. Receptor-mediated transcytosis, surface modification techniques, and biomimetic designs that enhance targeting effectiveness and biocompatibility are given particular attention. Furthermore, the review highlights key applications of nanoparticle-based systems in the management of major neurological disorders while critically addressing existing safety concerns, translational challenges, and regulatory limitations. Overall, this article underscores the potential of nanocarrier-based platforms to revolutionize CNS drug delivery and emphasizes future perspectives aimed at improving clinical translation and therapeutic outcome.

Keywords: Liposomes, Polymeric Nanoparticles, CNS Medication Delivery, Blood–Brain Barrier, And Neurological Illnesses.

1. INTRODUCTION

The central nervous system (CNS), which includes the brain and spinal cord, is protected by the blood–brain barrier (BBB), a highly specialized, dynamic structure that selectively permits substances to flow through. A balanced internal environment is necessary for the CNS to function at its best since it is crucial for controlling important body processes, cognition, behavior, and sensory processing. The blood flowing through the body and the delicate brain tissue of the central nervous system are protected by the blood-brain barrier [1-4].

The end-feet of astrocytes, pericytes, and a basement membrane support the densely connected capillary endothelial cells that make up the blood-brain barrier. Unlike capillaries present in other tissues, this unique anatomical arrangement restricts the free flow of chemicals from the bloodstream into the brain. As a result, only certain materials are permitted to pass through. By carefully regulating the flow of substances between the bloodstream and brain tissue, the blood–brain barrier (BBB), a highly specialized and dynamic interface, protects the central nervous system (CNS) It is made up of brain microvascular endothelial cells joined by tight junctions, pericytes, astrocytic end-feet, and a basement

membrane, all of which cooperate to maintain brain homeostasis by preventing pathogens and dangerous molecules from entering neural tissue while permitting the controlled movement of essential nutrients and ions. Normal neuronal function and the general health of the central nervous system depend on this selective barrier function [5, 6].

The BBB presents a major barrier to the transfer of therapeutic medications to the brain despite its vital protective function. Nearly all large-molecule medications and more than 98% of small-molecule treatments are prevented from entering due to its restrictive features. Treatment options for neurological conditions like Alzheimer's disease, Parkinson's disease, strokes, and brain tumors are severely limited by the concentrations of pharmacologically active compounds within the central nervous system (CNS) that are frequently attained through systemic administration. Drug bioavailability in the brain is further reduced by efflux transporters like P-glycoprotein, which actively remove medications from the brain and return them to the bloodstream [7–11].

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A promising substitute for enhancing medicine delivery across the blood-brain barrier is nanoparticles (NPs). Nanoparticles can successfully interact with the BBB's transport systems due to their nanoscale dimensions, changeable surfaces, and ability to encapsulate therapeutic substances. Nanoparticles can transport a variety of therapeutic payloads, such as small chemicals, biologics, and nucleic acids, directly to brain target areas by taking advantage of several blood–brain barrier (BBB) transport processes, such as receptor-mediated transcytosis and adsorptive-mediated transcytosis. Their nanoscale size, surface flexibility, and capacity to encapsulate therapeutic chemicals make this possible (Fig. 1). Their high surface-area-to-volume ratio protects against systemic degradation, improves drug stability, and permits targeted distribution, which may reduce side effects while increasing therapeutic efficacy [16–18].

The study provides a thorough review of recent developments and existing methods for medication delivery to the brain via nanoparticles. Driven by the swift advancement of nanotechnology and its revolutionary potential for CNS treatments, we focus on both proven and new approaches. Specifically, we outline both traditional and cutting-edge nanoparticle platforms intended to improve blood–brain barrier (BBB) penetration.

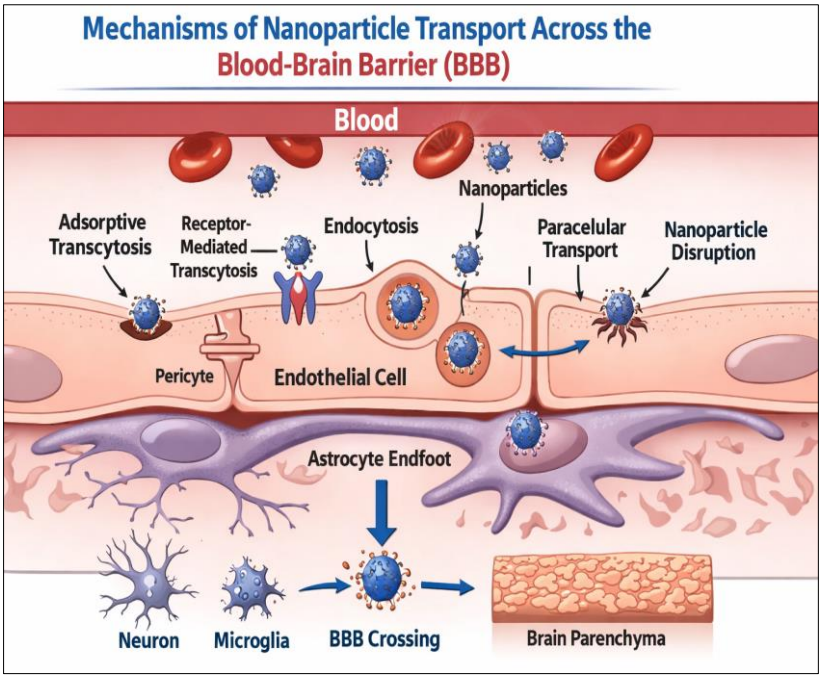

Figure 1: Mechanism of nanoparticle transport across blood-brain barrier

2. TYPES OF NANOPARTICLES USED IN BBB

2.1. Liposomes

Phospholipid bilayers generate liposomes, which are vesicles that can contain both lipid-soluble and water-soluble medicinal substances. Because of their structural resemblance to biological membranes, medications have improved stability, minimal toxicity, and great biocompatibility. Their circulation in the bloodstream is improved and receptor-mediated transport across the blood-brain barrier is made possible by surface modification with polyethylene glycol or particular targeting ligands, which increases their accumulation in the brain. These advantages make liposomes one of the most extensively studied and clinically useful nanocarriers for medication delivery to the central nervous system [19].

2.2. Nanoparticles Made of Polymers

Biodegradable polymers including PLGA, PEG, and chitosan are used to generate polymeric nanoparticles that protect encapsulated materials from early enzymatic breakdown while enabling regulated and prolonged drug release. To boost absorption across the blood-brain barrier and increase active targeting, their surfaces can be altered with antibodies, peptides, or ligands specific to receptors. These carriers are widely employed for the delivery of tiny chemicals, proteins, peptides, and nucleic acids to the brain because of their adaptable physicochemical properties and adaptability [20].

2.3. Solid Lipid Nanoparticles

By using solid lipids that are compatible with biological systems as their substrate, solid lipid nanoparticles combine the advantages of lipid-based and polymeric technologies. Particularly for lipophilic compounds, these systems offer enhanced permeability, controlled drug release, reduced toxicity, and increased stability. Enhanced penetration is made possible by their strong affinity for endothelial cell membranes. They become effective carriers for targeted delivery to the brain by passing through the blood-brain barrier [21].

2.4. Lipid Carriers with Nanostructures (NLCs)

A combination of solid and liquid lipids makes up nanostructured lipid carriers, a kind of second-generation lipid nanocarrier. This mixed composition improves the formulation's stability by increasing drug loading capacity and reducing medication loss during storage. NLCs are thought to be promising systems for novel treatments aimed at the central nervous system because they are more effective in delivering medications to the brain than conventional solid lipid nanoparticles [22].

2.5. Micelles Made of Polymers

Amphiphilic block copolymers spontaneously generate polymeric micelles, which are nanoscale structures. While the hydrophilic outer layer improves stability and prolongs bloodstream circulation duration, the hydrophobic core makes medications that are poorly soluble in water more soluble. They are particularly suitable for administering neurotherapeutic and anticancer drugs because of their small size and stealth features, which enable efficient blood-brain barrier penetration [19].

2.6. Dendrimers

Highly branching, tree-like polymers with a distinct architecture are known as dendrimers as well as other terminal functional groups. High drug loading and simple conjugation with targeted ligands are made possible by this structure. In addition to aiding accurate central nervous system therapy and possibly lowering systemic toxicity, their homogeneous nanoscale dimensions improve cellular absorption and focused distribution [20].

2.7. Metallic and Inorganic Nanoparticles

Gold, silica, and magnetic nanoparticles are examples of inorganic nanoparticles that have a variety of uses, including as imaging, magnetic targeting, and stimuli-responsive drug delivery. These characteristics make them easier to use in ranostic techniques that combine diagnostic and treatment on a single platform. These systems can be made for targeted administration, particularly when treating neurological disorders and brain malignancies [21].

2.8. Biomimetic Nanocarriers and Exosomes

Naturally occurring nanocarriers that can pass through the blood-brain barrier with minimal immunogenicity include exosomes and other vesicles made by cells. The efficient intracellular movement of medications, proteins, and genetic material is made possible by their biological origin. These biomimetic systems are becoming more widely acknowledged as cutting-edge platforms for effective, safe, and tailored medication delivery to the brain [22].

3. APPLICATIONS IN NEUROLOGICAL DISORDER

Clinical uses of nanoparticles are crucial for the early diagnosis and therapy monitoring of disorders including cancer and neurological diseases, as they improve patient care, survival, and quality of life. Additionally, they are an essential resource for both patients and medical professionals. Nanoparticles are being used more often to diagnose brain disorders or aid in drug delivery across the blood-brain barrier because of their many advantages, which include targeting

efficiency, non-invasiveness, biodegradability, stability, and controllability to load and release drugs [23, 24]. To provide a clear overview of the field, Table 1 summarizes key neurological disorders, their associated therapeutic challenges (particularly BBB penetration), the nanoparticle platforms or strategies employed, the delivered therapeutic agents, and the major outcomes achieved.

3.1. Brain Tumors

The current standard of care for brain tumors, according to Wang and Wu (2017), is a cautious surgical resection followed by oral temozolomide administration while receiving concomitant radiotherapy; nevertheless, this has not been able to effectively slow the disease's growth. There is an urgent need for innovative therapeutic approaches because adult primary brain tumors are among the most prevalent and fatal types. In recent years, polymeric nanoparticles containing the chemotherapeutic drug paclitaxel have been used, taking advantage of one of the few recognized biological characteristics of this type of tumor [25, 26].

Consequently, circulating nanoparticles containing paclitaxel could breach the blood-brain barrier and build up in the tumor. Similar initiatives that use carbon nanoparticles to encapsulate paclitaxel have been shown to improve the prognosis of head and neck tumors; however, no information on human subjects has been supplied. A doxorubicin administration method is presently being tested in human clinical studies with glioblastoma patients [22–27].

3.2. Alzheimer's Disease (AD)

Acetylcholinesterase inhibitors are the primary class of medications now used to treat AD. Blocking glutamatergic neurotransmission is another strategy; memantine is an NMDA-receptor antagonist. Since existing therapy methods only provide a slight improvement, there is clearly a need for new therapies. However, to prevent its severe first-pass metabolism and major side effects after oral treatment, the acetylcholinesterase inhibitor (rivastigmine) was loaded in SLN via nanotechnology. Due to its lipidic composition, rivastigmine-loaded SLN showed higher drug diffusion than drug solutions that included the drug's crystalline form. Antioxidants were also added to SLN as a possible AD treatment in an effort to enhance their brain biodistribution [23].

3.3. Cancer

Research has been done on the special biological ability of cancer metallic nanoparticles to induce autophagy and encourage cell death. Furthermore, biological metallic nanoparticles are cytotoxic substances that fight several types of cancer. The anticancer activity of biological NPs is mediated by three different ways. The first is the apoptotic pathway, which depends on a high concentration of ROS and causes oxidative stress and DNA fragmentation in the malignant cell. Second, because these nanomaterials can interfere with DNA to cause strand breaks, prevent replication, and impede repair mechanisms, as well as disrupt protein functions involved in cancer cell signaling, proliferation, and survival, proteins and DNA interference are critical to the anticancer activity of nanoparticles [30].

3.4. Stroke

The development of methods for both acute therapy and post-stroke recovery is essential because there are currently few stroke therapies. Polymeric nanoparticles, liposomes, metal and metal oxide nanoparticles, as well as inorganic and organic nanoparticles, are now being investigated for the treatment of stroke. According to one study, Lexiscan was enclosed in poly (lactic-co-glycolic acid) nanoparticles functionalized with chlorotoxin as a target ligand that may increase the blood-brain barrier's permeability. The system's promise for stroke treatment was demonstrated by the results, which revealed enhanced stroke survival [31–34].

3.5. Parkinson’s Disease

Parkinson's disease, which is associated with motor symptoms such rest tremor, bradykinesia, rigidity and postural instability, olfactory dysfunction, cognitive impairment, mental symptoms, and autonomic dysfunction, has been investigated using a variety of nanoparticle kinds. Several of these studies discussed the use of chitosan nanoparticles for the ex vivo delivery of two well-known anti-Parkinson medicines, pramipexole and selegiline [35, 36].

Table 1: Nanoparticle platforms for drug delivery across the blood–brain barrier (BBB) in neurological disorders: therapeutic challenges, strategies, delivered agents, and key outcomes [25-36]

Neurological Disorder	Therapeutic Challenge	Type of Nanoparticle/Strategy Used	Drug/Agent Delivered	Key Outcome/Advantage
Brain Tumors (Glioblastoma primary brain cancers)	Poor drug penetration across BBB: limited efficacy of surgery + radiotherapy + temozolomide	Polymeric Nanoparticles, carbon nanoparticles	Paclitaxel Doxorubicin	Enhanced BBB crossing, tumor accumulation Improved chemotherapeutic delivery, ongoing clinical testing

Neurological Disorder	Therapeutic Challenge	Type of Nanoparticle/Strategy Used	Drug/Agent Delivered	Key Outcome/Advantage
Alzheimer's Disease (AD)	First-pass metabolism: low brain drug levels, systemic side effects	Solid Lipid Nanoparticles (SLN); Lipid-based nanocarriers	Rivastigmine: Antioxidants	Improved brain biodistribution increased drug diffusion, reduced side effects, enhanced therapeutic efficiency
Cancer (general CINS-related tumors)	Drug resistance: need for selective cytotoxicity	Metallic/biological nanoparticles	Metallic anticancer agents	Induction of apoptosis, oxidative stress, DNA damage, inhibition of tumor cell proliferation
Stroke	Limited treatment options, poor BBB permeability of neuroprotective drugs	Polymeric nanoparticles (PLGA); Liposomes: Metal/metal oxide nanopartıcles	Lexiscan encapsulated	Improved BBB permeability, targeted delivery, enhanced survival outcomes in stroke models
Parkinson's Disease (PD)	Difficulty delivering dopaminergic drugs to brain; systemic toxicity	Chitosan nanoparticles	Prampexole; Selepiline	Enhanced brain delivery, improved ex vivo transport, better therapeutic targeting

5. SAFETY, CHALLENGES & LIMITATIONS

The blood-brain barrier (BBB), which carefully regulates the movement of chemicals into the brain, is a highly selective physiological barrier composed of interconnected endothelial cells, pericytes, and astrocyte end foot. This complex structure severely restricts the efficient transport of medications to the central nervous system (CNS) by blocking the entry of more than 98% of small molecules, biologics, antibodies, and therapies based on nanoparticles. Although procedures like targeted ultrasound and photothermal approaches can temporarily increase permeability, their safety for routine clinical usage is reduced since they require specialist equipment and may result in tissue injury or infection. Despite the development of ligand-functionalized and surface-modified nanoparticles to enhance receptor-mediated transcytosis, the mononuclear phagocyte system's rapid clearance of these particles and potential immunogenic reactions restrict their clinical use. Nanocarriers must avoid immune system detection and stay in circulation long enough to properly cross the blood-brain barrier (BBB). This combined difficulty frequently results in decreased brain accumulation and unsatisfactory therapeutic outcomes. The biological origins of the membrane-engineered nanoparticles used provide translation-related challenges. Animal or tumor cell-based systems are vulnerable to immune clearance and may elicit adverse immune reactions. Human cell membranes improve compatibility, but source issues, HLA matching, ethical issues, and restricted scalability hinder large-scale production. Furthermore, resource-intensive production techniques including extrusion, sonication, and microfluidics can damage membranes or result in batch-to-batch differences, making repeatability and regulatory body clearance more difficult [37].

Long-term biosafety is still not well characterized. Most studies do not fully evaluate pharmacokinetics, biodistribution, or longterm toxicity and instead use short-term animal models. The FDA and EMA have not yet formally approved any biomimetic membrane-coated nanoparticle therapy, thus manufacturing, ethical, and regulatory concerns still need to be addressed before clinical translation. Drug transport to the central nervous system is highly restricted by the BBB and the blood-cerebrospinal fluid barrier, which strictly regulate molecular interaction between the bloodstream and the brain. After systemic administration, only 2–5% of the dose typically reaches the central nervous system (CNS), which leads to subtherapeutic concentrations at target sites and increases the risk of off-target exposure and systemic side effects. Intrathecal administration can circumvent the blood-brain barrier by administering drugs directly into cerebrospinal fluid. However, there are a number of serious problems with this approach, including inadequate penetration into the brain parenchyma, unequal distribution throughout the central nervous system, difficulties in producing sustained drug release, and rapid clearance of active pharmaceutical ingredients because of continuous CSF turnover. Hydrophilic drugs are quickly excreted, whereas hydrophobic drugs may remain localized around the injection site.

Even if nanoparticles are proposed as a remedy for these issues, pharmacokinetic limitations persist. Glymphatic and microglial pathways eliminate a significant portion of intrathecally administered nanoparticles, shortening retention times and lowering therapeutic efficacy. Furthermore, optimizing nanoparticle size, charge, and surface properties for predictable biodistribution is still challenging, underscoring the fact that safe, efficient, and long-lasting CNS administration continues to be a significant translational problem [38].

6. FUTURE PERSPECTIVE

The BBB is crucial to the preservation of normal CNS function, and the development of certain brain disorders is linked to its disturbance. A deeper understanding of disease pathophysiology requires an understanding of the mechanism or mechanisms behind its control in both healthy and diseased brains. We now know a great deal about physical and molecular changes that go beyond the BBB breakdown in disease, even if it is still unclear what causes BBB dysfunction—either loss of CNS maintenance signals or breakdown signals from the pathological state. The development of targeted nanoparticle delivery strategies is made possible by the current understanding of BBB dysfunction, which is linked to the upregulated expression of particular receptors on brain capillary endothelial cells, such as the lactoferrin receptor (LfR) in Parkinson's disease (PD) and RAGE in Alzheimer's disease (AD). It is possible to create a plan for delivering medication into the damaged brain more successfully. Nanocarriers are tiny agents that can preserve pharmaceuticals by encapsulating them, extending their circulation period, and releasing their payload into the lesion site in a regulated manner both temporally and spatially following intravenous administration. Recently, some guiding principles have been identified to improve the transport of NP formulations via the BBB [39–41].

In order to advance this field of study toward possible clinical treatments, it is also crucial to address safety concerns. It is crucial to remember that the best NP formulations for brain delivery still build up considerably in other parts of the body, including the kidney, liver, and spleen, among other organs and tissues, before being excreted. Therefore, rather than releasing the medication in other parts of the body, it is crucial to create nano formulations that are only remotely activated once they reach the brain. The practical application of NPs in the field of regenerative medicine is anticipated to be made easier by upcoming advancements in triggerable nano formulations. The creation of nanoparticles that can target particular brain cells is another significant topic that merits more research [42].

7. CONCLUSION

Because of its selective permeability and tightly regulated transport processes, which significantly restrict the entry of the majority of therapeutic medicines into brain tissue, the blood-brain barrier (BBB) presents a major challenge in treating illnesses of the central nervous system. Conventional drug delivery techniques frequently fail to reach sufficient drug concentrations in the central nervous system (CNS), which results in poor treatment outcomes and increased systemic adverse effects. Because of this, nanotechnology-based drug delivery systems have emerged as viable substitutes that offer advantages like better drug stability, targeted delivery, longer circulation times, and improved transport across the blood-brain barrier through processes like receptor-mediated and adsorptive transcytosis. Numerous kinds of nanoparticles, such as inorganic, polymeric, lipid-based, and biomimetic exhibit significant promise for improving brain distribution and the efficacy of therapies for neurological diseases such brain tumors.

Despite the advancements, there are still a number of safety issues and translation challenges. Clinical use is still hampered by rapid immune clearance, poor penetration effectiveness, buildup in off-target organs, possible cytotoxic effects, and a lack of long-term biosafety data. The successful transition from preclinical research to clinical implementation is further hampered by pharmacokinetic issues, poor reproducibility, scaling issues, and regulatory constraints. These difficulties highlight the need for standardized production techniques, comprehensive toxicity evaluations, and improved design strategies to ensure safe and efficient delivery to the central nervous system.

Generally speaking, platforms that make use of nanoparticles provide a novel way to overcome obstacles associated with the blood-brain barrier (BBB) and hold great promise for future central nervous system (CNS) treatments. Closing the gap between experimental successes and clinical applications requires ongoing research focused on creating biocompatible materials, targeted distribution, controlled release mechanisms, and thorough safety assessments. Nanocarrier technologies have the potential to revolutionize drug delivery to the brain and significantly improve the treatment of neurological conditions with further development.

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