Nanoparticles as Game-Changers in Drug Delivery for Neurological Disorders

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ABSTRACT:
Nanoparticle-based drug delivery has emerged as a promising strategy for treating neurological disorders, overcoming the limitations of traditional drug delivery systems. The central challenge in this field lies in the effective targeting of the blood-brain barrier (BBB) and improving the bioavailability of drugs. This review explores the major neurological disorders, such as Alzheimer's, Parkinson's, and epilepsy, and the challenges involved in delivering therapeutic agents to the brain. We present an overview of nanoparticles, their types (lipid-based, polymeric, inorganic, dendrimers, and carbon-based), and their mechanisms for crossing the BBB. The review discusses how nanoparticles enhance the delivery of both allopathic drugs (e.g., levodopa, donepezil) and herbal compounds (e.g., curcumin, resveratrol) by improving solubility, bioavailability, and brain targeting. A comparative analysis of nanoparticle-based drug delivery for herbal versus synthetic drugs is provided, highlighting their complementary roles in combination therapy. Lastly, we review the clinical applications and future directions, emphasizing the integration of herbal and allopathic therapies in nanoparticle-based systems to revolutionize treatment strategies for neurological disorders.

1. Introduction

Neurological disorders encompass a broad spectrum of conditions, including Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, stroke, and multiple sclerosis (MS), which are among the most significant contributors to disability and mortality worldwide. According to recent estimates, neurological disorders affect hundreds of millions of individuals globally, with neurodegenerative diseases like AD and PD posing substantial healthcare and socio-economic challenges due to aging populations. Despite the availability of various therapeutic agents, the clinical outcomes of current treatments remain suboptimal, largely due to significant obstacles in delivering drugs effectively to the brain.

One of the most formidable challenges in treating neurological disorders is the blood-brain barrier (BBB), a tightly regulated interface that protects the brain from harmful substances but also impedes the passage of more than 98% of small molecules and nearly 100% of large therapeutic agents [1]. Conventional drug delivery systems often fail to overcome the BBB, leading to insufficient drug concentrations in the central nervous system (CNS). Additionally, issues such as drug instability, low bioavailability, rapid systemic clearance, and off-target effects further limit the therapeutic efficacy of traditional treatments for neurological disorders [2,3].

In recent years, nanotechnology has emerged as a transformative platform for addressing these challenges. Nanoparticles—nanoscale carriers that can encapsulate drugs or bioactive molecules—offer numerous advantages, such as enhanced drug solubility, controlled and sustained release, prolonged circulation time, and targeted delivery to specific sites, including the brain. Their ability to cross the BBB through mechanisms such as receptor-mediated endocytosis, adsorption-mediated transcytosis, and carrier-mediated transport makes them particularly well-suited for CNS drug delivery [4].

Nanoparticles have been extensively studied for delivering both synthetic (allopathic) and natural (herbal) therapeutic agents to treat neurological disorders. In allopathy, drugs such as levodopa (commonly used for Parkinson's disease), donepezil (used in Alzheimer’s disease), and anticonvulsants like phenytoin have been successfully incorporated into nanoparticle systems to improve their pharmacokinetics and therapeutic outcomes [5,6]. On the other hand, herbal medicines, which have been traditionally used for their neuroprotective properties, face limitations such as poor water solubility, rapid metabolism, and limited bioavailability. Nanoparticles have proven effective in overcoming these barriers, as demonstrated in the formulation of curcumin-loaded liposomes, resveratrol-loaded solid lipid nanoparticles, and Ginkgo biloba extract-loaded polymeric nanoparticles, all of which exhibit enhanced brain-targeting efficiency and therapeutic potential [7,8].

The integration of nanotechnology with both allopathic and herbal therapeutic approaches has opened new avenues for the treatment of neurological disorders. While allopathic drugs provide well-defined pharmacological mechanisms and rapid onset of action, herbal compounds offer the advantage of being multi-targeted and relatively safer. By combining these therapeutic modalities with nanotechnology, researchers aim to achieve synergistic effects, minimize adverse drug reactions, and optimize drug delivery to the CNS.

The purpose of this review is to provide a comprehensive overview of the current focus on both allopathic and herbal therapeutic agents. The review will highlight recent progress in nanoparticle formulations, their mechanisms of action in crossing the BBB, applications in specific neurological conditions, and the potential for clinical translation. Additionally, it will address the challenges and future prospects of this innovative approach, emphasizing its role in revolutionizing the treatment landscape for neurological disorders and inspiring future research in this interdisciplinary field.

Neurological Disorders and Their Drug Delivery Challenges

Neurological disorders refer to a diverse group of conditions that affect the central and peripheral nervous systems, often resulting in profound functional impairment, reduced quality of life, and significant socio-economic burdens. Among the most prevalent and debilitating disorders are Alzheimer’s disease (AD), Parkinson’s disease (PD), epilepsy, and multiple sclerosis (MS). This section provides an in-depth exploration of these disorders, their underlying mechanisms, and the challenges associated with delivering drugs to the central nervous system (CNS).

1. Major Neurological Disorders

a) Alzheimer's Disease (AD): is a progressive neurodegenerative disorder primarily affecting older adults. Its hallmark features include the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein in the brain. These pathological changes result in synaptic dysfunction, neuronal loss, and widespread neuroinflammation. The amyloid hypothesis suggests that Aβ accumulation triggers a cascade of events leading to oxidative stress, mitochondrial dysfunction, and neuronal apoptosis. Neuroinflammation, driven by activated microglia and astrocytes, exacerbates the damage [9,10]. Early symptoms include memory loss and difficulty performing routine tasks, progressing to severe cognitive and functional impairments such as loss of speech and inability to perform basic activities of daily living.

b) Parkinson's Disease (PD): is a movement disorder caused by the degeneration of dopaminergic neurons in the substantia nigra, a region of the midbrain. This leads to a reduction in dopamine levels in the striatum, disrupting motor control. The disease's pathology is marked by the presence of Lewy bodies, intracellular aggregates of alpha-synuclein protein, which interfere with normal cellular functions such as protein degradation and mitochondrial activity [11]. PD is characterized by motor symptoms, including bradykinesia (slowness of movement), resting tremors, muscle rigidity, and postural instability. Non-motor symptoms, such as depression, sleep disturbances, and autonomic dysfunction, are also common.

c) Epilepsy is a chronic neurological condition characterized by recurrent seizures resulting from abnormal electrical activity in the brain. This hyperexcitability is often linked to an imbalance between excitatory and inhibitory neurotransmission, typically involving glutamate and gamma-aminobutyric acid (GABA). Structural brain abnormalities, ion channel mutations, and neural circuit dysfunctions contribute to seizure generation and propagation [12]. Epileptic seizures manifest in various forms, ranging from brief lapses in attention (absence seizures) to convulsions, loss of consciousness, and sensory disturbances.

d) Multiple Sclerosis (MS): is an autoimmune disorder in which the immune system attacks the myelin sheath—the protective covering of neurons—resulting in demyelination, axonal damage, and neurodegeneration. This leads to impaired electrical signal conduction along affected neurons. The disease is believed to be triggered by a combination of genetic susceptibility and environmental factors, such as viral infections [13]. MS presents with a wide range of symptoms, including muscle weakness, impaired coordination, visual disturbances, fatigue, and cognitive deficits. The disease follows a relapsing-remitting or progressive course.

Challenges in Delivering Drugs to the CNS

The treatment of neurological disorders is hindered by unique physiological and pathological barriers, which limit the efficacy of conventional therapeutic approaches. These challenges are outlined below:

a) Blood-Brain Barrier (BBB): The BBB is a highly selective barrier composed of endothelial cells with tight junctions, astrocytic end-feet, and pericytes. It acts as a protective shield for the brain, maintaining homeostasis and preventing the entry of harmful substances. However, this selectivity also restricts the passage of most therapeutic agents, allowing only small, lipophilic molecules or those with specific transport mechanisms to enter the brain [14].Therapeutic agents, particularly hydrophilic drugs, peptides, proteins, and nucleic acids, face significant difficulty in crossing the BBB. For instance, monoclonal antibodies and gene therapies show great promise but are often rendered ineffective due to their inability to penetrate the BBB. These challenges necessitate the development of innovative delivery

strategies such as nanoparticle-based systems, which can enhance drug transport via receptor-mediated transcytosis or carrier-mediated transport [15].

b) Drug Stability and Metabolism: Many drugs are susceptible to rapid degradation or metabolism in the bloodstream before reaching the CNS. This instability limits their therapeutic efficacy and necessitates high systemic doses, increasing the risk of adverse effects. For example, dopamine, a key treatment target for Parkinson's disease (PD), cannot cross the BBB and is rapidly metabolized by enzymes like monoamine oxidase and catechol-O-methyltransferase [16]. Levodopa, a dopamine precursor, is used as an alternative, but it requires careful co-administration with enzyme inhibitors to improve its CNS bioavailability while minimizing peripheral side effects. Natural compounds like curcumin and resveratrol, which exhibit neuroprotective properties, also face challenges due to poor stability, rapid metabolism, and low bioavailability. Encapsulation in nanoparticles has been explored to address these issues, offering improved stability and controlled release [17].

c) Off-Target Effects: Systemic drug delivery often leads to non-specific distribution, causing adverse effects in non-target tissues. For example, anticonvulsants such as phenytoin and valproate, widely used for epilepsy management, can result in sedation, dizziness, and hepatotoxicity due to off-target actions [18]. Similarly, chemotherapeutic agents used for brain tumors often cause significant systemic toxicity. Nanoparticle-based drug delivery can mitigate these issues by enabling precise targeting of therapeutic agents to specific brain regions or cell types. Functionalized nanoparticles, decorated with ligands or antibodies, can bind to receptors uniquely expressed in diseased tissues, reducing systemic exposure and enhancing efficacy [19].

d) Limited Targeting and Drug Retention: Delivering drugs to specific brain regions or cell types, such as amyloid plaques in Alzheimer's disease (AD) or demyelinated neurons in multiple sclerosis (MS), is challenging due to the complexity of brain structure and the dynamic nature of CNS diseases. Even when drugs successfully cross the BBB, they often exhibit limited retention in the brain, reducing their therapeutic efficacy. Nanotechnology offers a promising solution through sustained-release formulations and bioadhesive nanoparticles, which prolong drug retention at the target site. For instance, lipid nanoparticles and polymeric carriers can be engineered to release drugs over extended periods, ensuring a consistent therapeutic effect [20].

e) Complexity of Disease Mechanisms: Neurological disorders are multifactorial, involving overlapping pathological processes such as oxidative stress, inflammation, mitochondrial dysfunction, and genetic mutations. For example, AD involves amyloid-beta toxicity, tau hyperphosphorylation, and neuroinflammation, while PD includes dopaminergic neuronal loss and alpha-synuclein aggregation [21]. Addressing these diverse mechanisms simultaneously requires combination therapies, which are difficult to formulate and deliver effectively. Nanoparticles provide a platform for co-delivering multiple therapeutic agents, enabling synergistic treatment of complex diseases. For instance, dual-drug-loaded nanoparticles can simultaneously target oxidative stress and inflammation, improving overall treatment outcomes [22].

f) Need for Non-Invasive Delivery: Invasive methods like intracranial injections, though effective, are not practical for routine clinical use due to risks such as infection, bleeding, and patient discomfort. Non-invasive delivery methods, such as nasal or oral routes, are preferred but face challenges related to low absorption, first-pass metabolism, and limited transport efficiency to the CNS [23]. Nasal delivery, in particular, has gained attention for bypassing the BBB through the olfactory and trigeminal nerve pathways. Nanoparticles designed for intranasal administration can improve drug absorption and transport directly to the brain, offering a non-invasive and patient-friendly alternative [24].

Nanotechnology offers innovative solutions to overcome the challenges of drug delivery to the CNS. Nanoparticles, owing to their unique physicochemical properties, have demonstrated significant potential in improving therapeutic outcomes. These nanosystems can enhance BBB penetration by being engineered to cross the barrier through receptor-mediated transport mechanisms, such as using transferrin or insulin receptors, or adsorption-mediated pathways. Liposomes and polymeric nanoparticles, loaded with therapeutic agents, have shown promise in facilitating brain delivery [25]. Encapsulation within nanoparticles also improves drug stability, protecting drugs from enzymatic degradation and prolonging systemic circulation time. This strategy has been particularly effective for natural compounds like curcumin and resveratrol, which suffer from poor stability and bioavailability in their free forms [26]. Furthermore, functionalized nanoparticles enable targeted delivery of drugs to specific brain regions or cell types, reducing off-target effects. For instance, nanoparticles coated with antibodies targeting amyloid-beta plaques in Alzheimer's disease (AD) have demonstrated enhanced therapeutic efficacy [27].

Nanoparticles also facilitate combination therapies by allowing the co-encapsulation of multiple drugs, such as synthetic and herbal compounds, within a single nano system. This approach enables synergistic treatment of multifactorial diseases like AD and has been explored using lipid-based and polymer-based nanoparticles [28]. Additionally, nanoparticle formulations can be designed for non-invasive administration through nasal or oral delivery routes, bypassing the BBB via the olfactory or trigeminal pathways. Mucoadhesive nanoparticles for intranasal delivery, for instance, have shown promising results in preclinical studies, offering a patient-friendly and efficient alternative to invasive methods [29].

Overview and Classification of Nanoparticles

Nanoparticles (NPs) are materials that range in size from 1 to 1000 nm and exhibit unique physicochemical properties due to their nanoscale size. They have become an important tool in drug delivery systems, particularly for treating complex conditions like neurological disorders. NPs can encapsulate both hydrophilic and hydrophobic drugs, enabling enhanced stability, controlled release, and targeted drug delivery to specific tissues or cells, such as brain tissue in the case of neurological disorders. Their small size allows for efficient penetration of biological barriers, such as the blood-brain barrier (BBB), making them ideal candidates for brain-targeted therapies.

Lipid-Based Nanoparticles: These are widely used in drug delivery systems, particularly for neurological disorders, because they can encapsulate both lipophilic and hydrophilic drugs. Liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions are the three main types.

Liposomes: They are spherical vesicles composed of phospholipid bilayers that can encapsulate drugs within their aqueous core or lipid bilayer. They are highly biocompatible and can be modified to increase their stability and ability to cross biological barriers like the BBB. Liposomes are often used to deliver drugs for Alzheimer's, Parkinson's, and other neurodegenerative diseases [30].

Solid Lipid Nanoparticles (SLNs): SLNs are solid at body temperature and are composed of a lipid core that can encapsulate both hydrophobic drugs and biologically active substances. They offer several advantages such as controlled drug release and protection from degradation. SLNs have shown potential in delivering drugs like paclitaxel and other therapeutic agents for neurological conditions [31].

Nanoemulsions: Nanoemulsions are fine emulsions with droplet sizes typically less than 100 nm. They are used to deliver hydrophobic drugs, enhancing their bioavailability. In neurological drug delivery, nanoemulsions can help in the efficient crossing of the BBB and release of active drugs in the brain [32].

Polymeric Nanoparticles: Polymeric nanoparticles are made from synthetic or natural polymers and can be designed to control drug release over extended periods, improve stability, and enhance bioavailability. They can be functionalized to improve targeting, especially for the delivery of drugs across the BBB.
PLGA Nanoparticles (Poly (lactic-co-glycolic acid)): PLGA is a biocompatible and biodegradable polymer used to produce nanoparticles with controlled release properties. PLGA nanoparticles can be used to deliver a range of drugs, including neuroprotective agents for diseases like Alzheimer's, Parkinson's, and multiple sclerosis [33].
Chitosan Nanoparticles: Chitosan, a natural polymer derived from chitin, is frequently used to prepare nanoparticles for drug delivery. It is biodegradable and non-toxic, making it a good candidate for delivery systems in neurological disorders. Chitosan nanoparticles can encapsulate drugs effectively and improve their solubility and stability [34].
PEGylated Systems: Polyethylene glycol (PEG) is often used to coat nanoparticles to improve their stability, reduce immunogenicity, and prolong circulation time in the bloodstream. PEGylated nanoparticles have been used to enhance brain targeting and delivery of drugs to treat neurological disorders [35].
Inorganic Nanoparticles: are composed of metals or metal oxides and have unique properties such as high surface area, magnetic response, and ability to conjugate with drugs or targeting ligands. These nanoparticles are particularly useful for imaging and drug delivery in neurological diseases.
Gold Nanoparticles: Gold nanoparticles (AuNPs) have excellent biocompatibility and ease of functionalization with targeting molecules. They have been studied for their potential to deliver therapeutic agents across the BBB and for imaging in neurological applications [36].
Silica Nanoparticles: Silica nanoparticles are widely used due to their surface tunability, high surface area, and stability. They can be functionalized to deliver drugs across the BBB and are useful in the treatment of neurological diseases [37].
Magnetic Nanoparticles: Magnetic nanoparticles are typically made of iron oxide and can be directed to specific locations in the body using an external magnetic field. This property is particularly useful for localized drug delivery to the brain in the case of neurological disorders [38].
Dendrimers and Carbon-Based Nanoparticles: Dendrimers are highly branched, nanoscale polymeric structures that offer excellent control over size and surface functionality. Their branched nature allows for high drug loading capacity and the possibility of functionalizing the surface for targeted delivery. Dendrimers have shown potential in delivering drugs to treat brain tumors, Alzheimer's, and other neurological disorders [39].
Carbon Nanotubes (CNTs): Carbon nanotubes, especially single-walled and multi-walled types, are hollow cylindrical structures with excellent mechanical properties and high surface area. They can be used for drug delivery in neurological disorders, as they have the ability to cross the BBB. CNTs can also be functionalized to target specific brain regions and improve therapeutic efficacy [40].
Graphene Oxide (GO): Graphene oxide is a two-dimensional carbon-based nanomaterial that is highly functionalizable. Its surface can be easily modified to carry therapeutic agents and facilitate their targeted delivery to the brain. GO has shown promise in drug delivery for neurological diseases, particularly for Parkinson’s and Alzheimer's disease [41].

Nanoparticles for Allopathic Drug Delivery

Bioavailability and Brain Targeting of Synthetic Drugs: Nanoparticles play a crucial role in enhancing the bioavailability and brain targeting of synthetic allopathic drugs used in the treatment of neurological disorders. These drugs, including levodopa, donepezil, phenytoin, diazepam, and methotrexate, often face significant challenges such as poor solubility, rapid

metabolism, and difficulty crossing the blood-brain barrier (BBB). By using various nanocarrier systems, these drugs can be encapsulated and delivered more effectively to their site of action, resulting in improved therapeutic outcomes.

Levodopa (Parkinson's Disease): Levodopa is commonly used to restore dopamine levels in the brain for Parkinson's disease treatment. However, it has limited bioavailability and is rapidly metabolized in the body. Using liposomes or polymeric nanoparticles to encapsulate levodopa enhances its stability and allows targeted delivery across the BBB, improving its therapeutic efficacy and reducing side effects [42].

Donepezil (Alzheimer's Disease): Donepezil is used to treat Alzheimer's disease by inhibiting acetylcholinesterase. However, its ability to cross the BBB and its first-pass metabolism limit its effectiveness. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been developed to encapsulate donepezil, improving its brain penetration, bioavailability, and providing sustained drug release, which enhances its cognitive-enhancing effects [43].

Phenytoin (Epilepsy): Phenytoin, an anticonvulsant drug, faces challenges related to its poor solubility and limited ability to penetrate the BBB. By encapsulating phenytoin in polymeric nanoparticles and lipid nanocarriers, its solubility is improved, leading to better bioavailability, controlled release, and more effective treatment of epilepsy with fewer side effects [44].

Diazepam (Anxiety and Seizure Disorders): Diazepam is an anxiolytic and anticonvulsant drug but suffers from rapid metabolism and side effects. Nanocarriers such as nanostructured lipid carriers (NLCs) and polymeric nanoparticles offer improved solubility and enhanced brain targeting, thereby increasing the drug's therapeutic effect while reducing side effects [45].

Methotrexate (Cancer Treatment): Methotrexate is a chemotherapy drug that is often used to treat cancer. However, it is associated with significant toxicity due to its non-selective distribution. Liposomal and polymeric micelles formulations of methotrexate help to selectively deliver the drug to tumor cells while reducing systemic toxicity, improving therapeutic outcomes in cancer treatment [46].

3. Nanoparticles for Herbal Drug Delivery

Limitations of Herbal Compounds Herbal compounds, despite their therapeutic potential, often face limitations such as poor solubility, low bioavailability, and difficulty in crossing the BBB. By incorporating these compounds into nanoparticle formulations, it is possible to enhance their solubility, stability, and bioavailability. This makes herbal drugs more effective in treating neurological disorders.

Curcumin (Anti-inflammatory, Antioxidant): Curcumin, derived from turmeric, is a potent antioxidant and anti-inflammatory compound. However, its low solubility and bioavailability hinder its clinical application. Nanoparticles such as PLGA nanoparticles and liposomes have been developed to improve curcumin's bioavailability, stability, and brain penetration, enhancing its neuroprotective and anti-inflammatory effects [47]. Resveratrol (Antioxidant, Anti-aging): Resveratrol, found in red wine, is known for its neuroprotective effects, but its bioavailability is poor. Encapsulating resveratrol in liposomes and polymeric nanoparticles increases its solubility and brain penetration, allowing for sustained therapeutic effects in treating neurodegenerative diseases like Alzheimer's and Parkinson's [48].

Ginkgo Biloba (Cognitive Enhancement, Antioxidant): Ginkgo biloba has been used traditionally to enhance cognitive function. However, its poor bioavailability and limited brain penetration restrict its effectiveness. Nanoemulsions and nanostructured lipid carriers (NLCs) have been shown to improve Ginkgo biloba's bioavailability and delivery to the brain, enhancing its cognitive and neuroprotective effects [49].

Bacopa Monnieri (Memory Enhancement, Neuroprotective): Bacopa monnieri is traditionally used as a memory enhancer. Nanoparticles such as solid lipid nanoparticles (SLNs) and liposomes are used to encapsulate Bacopa, improving its solubility and bioavailability, which enhances memory and cognitive function and provides neuroprotection in conditions like Alzheimer's [50].
Ashwagandha (Adaptogen, Stress Reduction): Ashwagandha is a well-known adaptogen that helps reduce stress and improve cognitive function. By encapsulating it in polymeric nanoparticles and liposomes, its bioavailability and brain-targeting ability are enhanced, allowing for better stress management and neuroprotection [51].
Green Tea Extract (Antioxidant, Anti-inflammatory): Green tea extract is rich in polyphenols such as EGCG, which have potent antioxidant and anti-inflammatory properties. Encapsulating these compounds in polymeric micelles or nanoparticles helps improve their solubility, bioavailability, and brain penetration, offering enhanced neuroprotection [52].
Gotu Kola (Cognitive Function, Anti-anxiety): Gotu kola has been traditionally used to improve cognitive function and reduce anxiety. By formulating nanoemulsions and liposomes, the bioavailability and stability of Gotu kola's active components are enhanced, improving cognitive function and providing neuroprotective effects [53]

Table 1: Types of Nanoparticles for Drug Delivery

Drug	**Type of Nanoparticle**	**Mechanism of Action**	**Outcome**
Levodopa	Liposomes, Polymeric Nanoparticles	Encapsulation improves solubility, stability, and brain penetration.	Increased bioavailability and therapeutic effect in Parkinson's disease.
Donepezil	Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs)	Enhances brain penetration, reduces first-pass metabolism, and provides sustained release.	Improved cognitive function, prolonged therapeutic effect in Alzheimer's.
Phenytoin	Polymeric Nanoparticles, Lipid Nanocarriers	Controlled release, improved bioavailability, and BBB penetration.	Improved seizure control in epilepsy treatment.
Diazepam	Nanostructured Lipid Carriers (NLCs), Polymeric Nanoparticles	Increases solubility, reduces rapid metabolism, and enhances brain targeting.	Reduced side effects, improved anti-anxiety and anticonvulsant effects.
Methotrexate	Liposomes, Polymeric Micelles	Enhances solubility and selective delivery to tumor sites, reducing systemic toxicity.	Improved efficacy with minimized side effects in cancer treatment.
Curcumin	PLGA Nanoparticles, Liposomes	Increases solubility and stability, enhances brain penetration for	Reduced oxidative stress, improved neuroprotection in neurodegenerative

		neuroprotection.	diseases.
Resveratrol	Liposomes, Polymeric Nanoparticles	Increases solubility, brain penetration, and sustained release.	Enhanced neuroprotection in Alzheimer's and Parkinson's.
Ginkgo Biloba	Nanoemulsions, Nanostructured Lipid Carriers (NLCs)	Improves bioavailability and BBB penetration.	Enhanced cognitive function and neuroprotection.
Bacopa Monnieri	Solid Lipid Nanoparticles (SLNs), Liposomes	Improves solubility, bioavailability, and memory-enhancing effects.	Enhanced memory, neuroprotection in neurodegenerative diseases.
Ashwagandha	Polymeric Nanoparticles, Liposomes	Enhances bioavailability, brain targeting, and neuroprotective effects.	Improved stress management, neuroprotection, reduced anxiety.
Green Tea Extract	Polymeric Micelles, Nanoparticles	Improves solubility and brain penetration.	Enhanced neuroprotection, anti-inflammatory effects.
Gotu Kola	Nanoemulsions, Liposomes	Enhances solubility and bioavailability, improving cognitive function.	Enhanced cognitive function, anti-anxiety effects.

Comparative Analysis: Herbal vs. Allopathic Approaches

Nanoparticle-based drug delivery has emerged as a powerful strategy for enhancing the therapeutic efficacy of both herbal and allopathic drugs. Herbal drugs, often complex mixtures of bioactive compounds, can benefit from nanoparticle encapsulation, which improves bioavailability, solubility, and targeted delivery while minimizing off-target effects. These nanoparticles, such as liposomes or PLGA (poly (lactic-co-glycolic acid)), are biodegradable and biocompatible, making them suitable for natural compounds. However, challenges such as poor solubility of certain herbal compounds and regulatory hurdles remain. On the other hand, allopathic drugs, which are typically well-studied and highly potent, can also benefit from nanoparticle formulations that enhance bioavailability, stability, and targeted delivery.

Nanoparticles allow for controlled release and protection of sensitive drugs, improving therapeutic outcomes, especially in diseases like cancer and neurological disorders. However, allopathic drugs may present issues like toxicity, cost, and the potential for drug resistance. When used together in combination therapy, herbal and allopathic drugs can complement each other, enhancing the efficacy of treatment while reducing side effects. For example, herbal drugs with antioxidant or anti-inflammatory properties can mitigate the side effects of chemotherapy or other allopathic treatments. Despite the promise of such combination therapies, challenges in formulation compatibility, regulatory approval, and production costs must be addressed. Overall, nanoparticle-based delivery systems offer significant potential for both enhancing the therapeutic effects of herbal and allopathic drugs and achieving a synergistic approach in combination therapy [54-55]

Mechanism of nanapoarticle

The blood-brain barrier (BBB) serves as a selective permeability barrier that protects the brain from harmful substances. However, it also poses a significant challenge for drug delivery to the brain. Nanoparticles can cross the BBB through several mechanisms. One approach is via transcellular transport, where nanoparticles are able to pass through endothelial cells by endocytosis, a process where the cell engulfs the nanoparticles into vesicles, which are then transported across the barrier. Another method is paracellular transport, where nanoparticles pass between the tight junctions of the endothelial cells. Additionally, nanoparticles can be engineered to exploit receptor-mediated transcytosis, where nanoparticles functionalized with ligands targeting specific receptors (e.g., transferrin, insulin) on the endothelial cells can bind to receptors, triggering cellular uptake and transport into the brain. This receptor-targeted mechanism enhances the specificity and efficiency of drug delivery to the brain [56].

Passive Targeting vs. Active Targeting

Nanoparticle drug delivery systems can utilize two distinct targeting strategies: passive targeting and active targeting. Passive targeting relies on the natural properties of nanoparticles, such as size, shape, and surface charge, to exploit the enhanced permeability and retention (EPR) effect. Tumor tissues, inflamed areas, and sites with disrupted vasculature tend to have leaky blood vessels, allowing nanoparticles to accumulate in these regions more effectively than in normal tissues. The EPR effect is also utilized in non-tumor diseases with similar vascular characteristics, such as in certain brain disorders.Active targeting involves functionalizing the nanoparticle surface with specific ligands, antibodies, or peptides that recognize and bind to particular biomolecules or receptors overexpressed on the target cells. This targeting strategy enhances the specificity and efficiency of drug delivery to diseased tissues or organs, reducing the side effects of drugs on healthy tissues [57].

Drug Loading, Release Mechanisms, and Biodegradability

The drug loading capacity of nanoparticles refers to the amount of therapeutic agent that can be incorporated into the nanoparticle system, which depends on the nature of both the drug and the nanoparticle. Drugs can be encapsulated within the core of nanoparticles (e.g., liposomes, micelles) or adsorbed onto their surface. The drug loading efficiency plays a crucial role in ensuring that sufficient quantities of the drug reach the target site.

The release mechanisms of drugs from nanoparticles include diffusion, degradation, and swelling. In diffusion-controlled release, drugs diffuse out of the nanoparticle matrix over time. In degradable nanoparticles, the drug is released as the nanoparticle itself degrades, either through enzymatic cleavage or environmental changes such as pH or temperature. In swelling-controlled release, the nanoparticles swell in response to changes in environmental conditions, leading to the release of the drug. The biodegradability of nanoparticles ensures that after drug release, the nanoparticles break down into non-toxic byproducts, avoiding the accumulation of foreign materials in the body. Biodegradable materials like poly (lactic-co-glycolic acid) (PLGA) are commonly used in nanoparticle formulations due to their controlled degradation profiles [58].

Applications in Neurological Disorders

Nanoparticle-based drug delivery systems are emerging as highly effective tools for treating neurological disorders, including Alzheimer's, Parkinson's, epilepsy, and other conditions. These systems enhance drug bioavailability, target specific areas in the brain, and minimize side effects. For Alzheimer's disease, nanoparticles like liposomes and dendrimers have been used to deliver amyloid-beta (Aβ) inhibitors and antioxidants, aiming to reduce Aβ plaques and oxidative stress. In Parkinson's disease, nanoparticles such as solid lipid nanoparticles

(SLNs) and polymeric nanoparticles are used to deliver dopamine or dopamine agonists to the brain, overcoming the blood-brain barrier (BBB). For epilepsy, nanoparticles have been used to deliver antiepileptic drugs (AEDs), such as valproic acid, directly to the brain, ensuring therapeutic concentrations at the site of action. In addition, these drug delivery systems can also be used for the treatment of other neurological disorders like multiple sclerosis and Huntington's disease by targeting specific areas of the brain and spinal cord to deliver neuroprotective drugs.

Herbal drugs have also gained attention in nanoparticle-based drug delivery for neurological disorders. For example, nanoparticles can encapsulate curcumin, an active component of turmeric, to enhance its bioavailability and potential therapeutic effects in Alzheimer's and Parkinson's disease by acting as an anti-inflammatory and antioxidant agent. Similarly, nanoparticles made from natural polymers have been used to deliver ginsenosides from ginseng, which are believed to have neuroprotective effects. Nanoparticle formulations of resveratrol, found in red wine, have shown promise in preventing neurodegeneration in Alzheimer's and other neurodegenerative diseases[59-60].

Challenges and Future Directions

One major challenge in the formulation of nanoparticle-based drug delivery systems for herbal drugs is the standardization of these formulations. Herbal drugs contain multiple active compounds with varying levels of bioavailability, which complicates the consistency of drug delivery. The lack of established protocols for extraction, quality control, and formulation leads to issues related to dose standardization and reproducibility, especially when combined with synthetic drugs in nanoparticle systems. Additionally, the potential for herbal compounds to interact unpredictably with synthetic drugs must be carefully evaluated to ensure that such combinations do not reduce efficacy or cause toxicity [61].

Future research should focus on optimizing the formulation of nanoparticles to improve the stability, release profiles, and targeted delivery of both herbal and synthetic drugs. Moreover, the integration of herbal and allopathic therapies in nanoparticle-based systems holds substantial promise for enhancing treatment efficacy. The synergy between the anti-inflammatory, antioxidant, and neuroprotective properties of herbal drugs and the specific action mechanisms of synthetic drugs can be effectively harnessed to combat neurological disorders. These integrated therapies could help to address the multifaceted nature of such diseases, leading to improved patient outcome.

Table 2: Examples of Nanoparticle-Based Drug Delivery Systems for Neurological Disorders

Allopathic Drugs	Enhances bioavailability, bypasses BBB, targets brain regions	1. Donepezil (Alzheimer's)	Alzheimer's Disease
		2. Levodopa (Parkinson's)	Parkinson's Disease
		3. Valproic Acid (Epilepsy)	Epilepsy
		4. Rivastigmine (Alzheimer's)	Alzheimer's Disease
		5. Baclofen (Spasticity)	Multiple Sclerosis, Spinal Cord Injury
Herbal Drugs	Neuroprotective, antioxidant, anti-inflammatory properties	1. Curcumin (Turmeric)	Alzheimer's, Parkinson's Disease
		2. Ginsenosides (Ginseng)	Parkinson's Disease, Cognitive Decline

		3. Resveratrol (Red Wine)	Neurodegenerative Diseases
		4. Withanolides (Ashwagandha)	Stress, Cognitive Impairment
		5. Huperzine A (Huperzia)	Alzheimer's Disease

2. Conclusion

Nanoparticle-based drug delivery represents a transformative approach in the treatment of neurological disorders, addressing key challenges like the blood-brain barrier (BBB) and poor drug bioavailability. The ability of nanoparticles to enhance the delivery of both allopathic and herbal drugs opens new possibilities for more effective therapies. In the case of allopathic drugs, nanoparticles improve the targeted delivery of compounds like levodopa and donepezil, ensuring better efficacy in conditions like Parkinson's and Alzheimer's. For herbal drugs, nanoparticles overcome limitations such as low solubility and poor bioavailability, allowing for improved therapeutic outcomes, as seen with compounds like curcumin and resveratrol. Moreover, combining herbal and allopathic treatments through nanoparticle systems offers a holistic approach that could address multiple aspects of neurological diseases simultaneously, enhancing treatment efficacy. Despite the promising potential, challenges remain in terms of standardization, formulation, and clinical translation, particularly for herbal nanoparticle systems. Continued research is needed to optimize these delivery systems, with a focus on safety, scalability, and regulatory approval. As these challenges are addressed, nanoparticle-based drug delivery could revolutionize the treatment landscape for neurological disorders, offering more targeted, effective, and personalized therapies for patients.

3. References

1. Singh SK, Bhardwaj A, Sharma S, Sati P, Kumar S, Das S. Emerging role of nanotechnology in therapeutics of neurological disorders: Advances and challenges. *Life Sci*. 2021;277:119609. doi:10.1016/j.lfs.2021.119609
2. Vashist A, Kaushik A, Ahmad S, Nair M. Nanotechnology-based drug delivery systems for the treatment of neurological disorders. *Mater Today Chem*. 2018;7:102-109. doi:10.1016/j.mtchem.2018.01.006
3. Pardridge WM. Drug transport across the blood-brain barrier. *J Cereb Blood Flow Metab*. 2012;32(11):1959–1972. doi:10.1038/jcbfm.2012.126
4. Sharma K, Choudhary N, Soni VK. Nanoparticles for neurological disorders: A recent update on therapeutic strategies. *Crit Rev Ther Drug Carrier Syst*. 2023;40(3):151-179.
5. Jain A, Jain SK. Nanotechnology-based drug delivery systems for the treatment of neurological disorders. *Adv Drug Deliv Rev*. 2018;129:1-29. doi:10.1016/j.addr.2017.09.007
6. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of nanotechnology-based formulations. *J Control Release*. 2021;337:527-570. doi:10.1016/j.jconrel.2021.08.026
7. Feng T, Wei Y, Lee RJ, Zhao L. Liposomal and nanoparticle formulations of curcumin for therapeutic applications in neurological diseases. *J Nanomater*. 2019;2019:1-15. doi:10.1155/2019/4941034

8. Misra S, Shahiwala A. Drug delivery to the central nervous system: A review. *J Pharm Pharm Sci*. 2013;16(2):237-273. doi:10.18433/j35s3r
9. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nat Rev Dis Primers. 2015;1:15056. doi:10.1038/nrdp.2015.56
10. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science. 2002;297(5580):353-356.
11. Dauer W, Przedborski S. Parkinson's disease: Mechanisms and models. Neuron. 2003;39(6):889-909.
12. Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov. 2013;12(10):757-776. doi:10.1038/nrd4126
13. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372(9648):1502-1517.
14. Pardridge WM. Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab. 2012;32(11):1959–1972. doi:10.1038/jcbfm.2012.12.
15. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of nanotechnology-based formulations. J Control Release. 2021;337:527-570. doi:10.1016/j.jconrel.2021.08.026
16. Dauer W, Przedborski S. Parkinson's disease: Mechanisms and models. Neuron. 2003;39(6):889-909.
17. Sharma RA, Steward WP, Gescher AJ. Pharmacokinetics and pharmacodynamics of curcumin. Adv Exp Med Biol. 2007;595:453-470.
18. Löscher W. Drug resistance in epilepsy: Clinical impact, potential mechanisms, and new innovative treatment options. Pharmacol Rev. 2017;69(1):68-100.
19. Jain A, Jain SK. Nanotechnology-based drug delivery systems for the treatment of neurological disorders. Adv Drug Deliv Rev. 2017;129:1-4.
20. Saraiva C, Praca C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release. 2016;235:34-47. doi:10.1016/j.jconrel.2016.05.04
21. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science. 2002;297(5580):353-356.
22. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez-Torres MP, Acosta-Torres LS, et al. Nano based drug delivery systems: Recent developments and future prospects. J Nanobiotechnol. 2018;16:71. doi:10.1186/s12951-018-0392-8
23. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective—a review. Drug Deliv Transl Res. 2013;3(1):42-62.
24. Illum L. Nasal drug delivery—recent developments and future prospects. J Control Release. 2012;161(2):254-263. doi:10.1016/j.jconrel.2012.01.024
25. Zhang Y, Liu X, Li C, et al. Nanoparticle-based drug delivery systems for CNS diseases: From concepts to clinical applications. Nanomedicine. 2020;15(3):345-366.
26. Singh R, Rana S, Sinha V, et al. Nanoparticle delivery systems for curcumin: Challenges and applications. Curr Drug Deliv. 2019;16(1):21-34.
27. Jiang Z, Li T, Zhao J, et al. Antibody-coated nanoparticles for targeted delivery in Alzheimer's disease therapy. J Control Release. 2021;331:150-160.
28. Patel K, Soni S, Patel S, et al. Lipid and polymer-based nanoparticle formulations for combinational therapies in Alzheimer's disease. J Nanosci Nanotechnol. 2021;21(4):2045-2059.

29. Yadav, S. et al. (2021). *Liposome-based Drug Delivery Systems in Neurological Diseases: An Overview*. Drug Development and Industrial Pharmacy, 47(1), 8-19.
30. Patel, K. et al. (2019). *Solid Lipid Nanoparticles for Brain Targeting Drug Delivery in Neurodegenerative Diseases*. European Journal of Pharmaceutical Sciences, 134, 20-29.
31. Rathod, P. et al. (2022). *Nanoemulsions in Neurodrug Delivery: Formulation and Applications*. Advanced Drug Delivery Reviews, 183, 114159.
32. Zhang, H. et al. (2021). *Polymeric Nanoparticles for Brain Drug Delivery: Challenges and Opportunities*. Nanomedicine, 16(4), 321-335.
33. Ali, S. et al. (2021). *Chitosan-based Nanoparticles for Drug Delivery Applications in Neurology*. Journal of Drug Targeting, 29(3), 254-269.
34. Torchilin, V. P. (2014). *Polyethylene Glycol-based Micelles and Nanoparticles for Drug Delivery: Opportunities and Challenges*. Biochemical Pharmacology, 87(1), 63-79.
35. Saha, K. et al. (2020). *Gold Nanoparticles in Drug Delivery: Opportunities and Challenges in Neurology*. Drug Discovery Today, 25(10), 1832-1840.
36. Bhunia, S. et al. (2019). *Silica Nanoparticles for Neurotherapeutic Applications: Mechanisms and Recent Developments*. Nanomedicine, 14(4), 483-497.
37. Muzammil, S. et al. (2020). *Magnetic Nanoparticles: Potential Applications in Neurodegenerative Diseases*. Biomaterials, 232, 119723.
38. Bhatt, P. et al. (2021). *Dendrimers in Drug Delivery: A Review of Mechanisms and Applications in Neurological Disorders*. Journal of Controlled Release, 332, 122-137.
39. Li, Y. et al. (2019). *Carbon Nanotubes in Brain Drug Delivery: Recent Developments and Future Prospects*. Journal of Drug Delivery Science and Technology, 52, 720-730.
40. Zhu, W. et al. (2021). *Graphene Oxide in Drug Delivery and Neurological Disorders*. Materials Science and Engineering: C, 120, 111654.
41. Wang X, Zhang H, Sun H, et al. Mucoadhesive nanoparticle formulations for intranasal drug delivery to the brain. Pharmaceutics. 2021;13(11):1886.
42. Zhang Y, et al. Levodopa-loaded liposomes for improved delivery across the blood-brain barrier. Neuropharmacology. 2022; 182: 108285.
43. Singh M, et al. Nanoparticle-based drug delivery of donepezil: An efficient approach for Alzheimer's therapy. International Journal of Nanomedicine. 2020; 15: 3701-3712.
44. Jiang Y, et al. Polymeric nanoparticles for anticonvulsant drug delivery: Enhancing the therapeutic effects. Drug Delivery and Translational Research. 2019; 9(6): 931-944.
45. Ranjan S, et al. Liposomal formulation of levodopa for targeted delivery to the brain. Journal of Drug Targeting. 2021; 29(1): 37-44.
46. Shah V, et al. Clinical evaluation of donepezil-loaded NLCs in Alzheimer's disease: A promising approach. Frontiers in Pharmacology. 2020; 11: 570361.
47. Panda A, et al. Nanoparticles for curcumin delivery in neurodegenerative diseases: Therapeutic implications. Frontiers in Pharmacology. 2020; 11: 561125.
48. Choi Y, et al. Nanoparticle-based delivery of resveratrol for neuroprotection. Journal of Nanoscience and Nanotechnology. 2019; 19(3): 1571-1581.
49. Zhao X, et al. Nanoemulsions of Ginkgo biloba for enhanced brain targeting: A promising strategy for cognitive improvement. Journal of Ethnopharmacology. 2020; 248: 112343.
50. Sharma M, et al. Bacopa Monnieri nanoparticles enhance cognitive function in Alzheimer's disease models. Journal of Controlled Release. 2020; 323: 12-24.
51. Kaur R, et al. Liposomal Ashwagandha enhances neuroprotection and reduces anxiety. Journal of Ethnopharmacology. 2021; 276: 114137.

52. Zhang Y, et al. Polymeric micelles for green tea polyphenol delivery in the brain. Journal of Drug Delivery Science and Technology. 2021; 64: 102556.
53. Kumar S, et al. Gotu Kola nanocarriers enhance cognitive function and reduce anxiety. Neurotherapeutics. 2019; 16(4): 1314-1324.
54. Sahoo, S. K., Parveen, S., & Panda, J. J. (2011). The present and future of nanotechnology in human health care. Nanomedicine: Nanotechnology, Biology and Medicine, 7(1), 1-20.
55. Zhuang, X., Deng, Z. B., & Mu, J. (2015). Nanoparticle-based drug delivery systems in cancer treatment. Frontiers in Pharmacology, 6, 135.
56. Kroll, K., et al. (2018). The blood-brain barrier and its role in nanomedicine. Pharmacological Research, 129, 111-122. https://doi.org/10.1016/j.phrs.2018.01.003.
57. Danhier, F., et al. (2012). Nanoparticle-mediated drug delivery: The challenges and potential for cancer therapy. Journal of Controlled Release, 161(2), 277-290. https://doi.org/10.1016/j.jconrel.2012.03.020.
58. Zhang, L., et al. (2019). Nanoparticle-based drug delivery systems: A comprehensive review of biomedical applications. Journal of Controlled Release, 308, 48-65. https://doi.org/10.1016/j.jconrel.2019.06.010.
59. Patel, A., et al. (2023). "Nanoparticle-based drug delivery systems in neurological disorders: A review." *Journal of Drug Delivery Science and Technology*, 61: 102272.
60. Singh, R., et al. (2021). "Nanomedicine in neurodegenerative diseases: Recent advancements and future directions." *Advanced Drug Delivery Reviews*, 178: 44-60.
61. Liu, Y., et al. (2022). "Nanoparticles for brain-targeted drug delivery: Recent advances and future challenges." *Journal of Controlled Release*, 349: 301-315.