Frontiers in Health Informatics ISSN-Online:2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 3
Open Access

Advancements in the Controlled Delivery of Nanodrugs to the Central Nervous System: Challenges and Innovations

[1]Dr C. sundara moorthi *,Dr. R. Gayathri [2] Dr B.R. Srinivasmurthy, [3]Dr.Anjaneyulu Vinukonda, [4]Dr A. Dineshraja ,[5]M. Dinesh mani, [6]Naveen Yadav JK ,[7]Dr.S. Muthukumar

[1]Associate Professor, Dept of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, Tamilnadu
[2]Assistant Manager, Forumation Research and Development, Maiva Pharma Pvt Ltd, Hosur, Tamilnadu
[3]Scientist-Formulation and Process Development, Strides Pharma Inc, New York, USA
[4]Assistan Professor, Dept of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, Tamilnadu
[5]Assistant Professor, Faculty of Pharmacy, Karpagam Academy of Higher education, Coimbatore, Tamilnadu
[6]Assistant Professor, United College of Pharmacy, Coimbatore, Tamilnadu
[7]Manager, Formulation Research and Development, Maiva Pharma Pvt Ltd, Hosur, Tamilandu
*Corresponding Author
Dr. R. Gayathri,
Professor-Dept of Pharmaceutics,
KMCH College of Pharmacy,
Coimbatore, Tamilnadu
Email: gayathrigogul@gmail.com

Cite this paper as: C. sundara moorthi R. Gayathri ,B.R. Srinivasmurthy,Anjaneyulu Vinukonda, A. Dineshraja ,M. Dinesh mani, Naveen Yadav JK ,S. Muthukumar (2024) Advancements in the Controlled Delivery of Nanodrugs to the Central Nervous System: Challenges and Innovations. *Frontiers in Health Informatics, 13* (3),9401-9416

Abstract

About 1 million of the 6.8 million deaths attributed to disorders of the central nervous system (CNS) each year are caused by neurodegenerative diseases, which include Parkinson's disease, Alzheimer's disease, tumours, and ischaemic stroke. Because of the intricacy of the brain, CNS issues are a major concern. To address issues with toxicity, specificity, and delivery, several drugs are available to treat illnesses of the central nervous system (CNS). Therapeutic drugs are challenged by barriers such as the blood-brain barrier (BBB), which prevents them from reaching their intended target. Scholars have been investigating pathways for pharmaceuticals to cross the blood-brain barrier and get to their intended targets. These issues show how different cellular processes must be changed or manipulated by nanotechnology to obtain the required properties. Nanoparticles are an efficient replacement for drug delivery and other methods because of their nano size, which allows them to cross the blood-brain barrier. Effective drug transfer and enhanced CNS disease treatment and diagnosis are possible using nanotechnology. Drugs could be altered via nanoengineering to carry out tasks like transferring across the blood-brain barrier, modifying signaling pathways, focussing on certain cells, facilitating efficient gene transfer, and encouraging nerve cell regeneration and preservation.

Keywords: *Neurodegenerative disorders, Central nervous system, Blood-brain barrier, Nanotechnology, Drug delivery*

Introduction

Brain cancer and other central nervous system (CNS) and peripheral nervous system (PNS) disorders are among the most common, lethal, and undertreated medical illnesses. In certain pathological conditions, such as stroke, Alzheimer's disease (AD), diabetes, Parkinson's disease (PD), seizures, and amyotrophic lateral sclerosis (ALS), the blood-brain barrier (BBB) is disrupted. To combat brain diseases, there will need to be a significant increase in drug development worldwide over the next 20 years due to the growing number of older people and teenagers with

CNS issues [1]. Drug discovery for brain disorders has the lowest success rate when compared to all other pharmacological formulations. Compared to non-CNS pharmaceuticals, the development of CNS drugs takes a lot longer [2].

A group of illnesses that primarily impact individual neurons within the neural network are together referred to as "neurodegenerative diseases." The fundamental component of the nervous system, which mostly guards the spinal cord, is a network of neurons. The body cannot repair neurons because they generally do not replicate or renew on their own; therefore, when a neuron is damaged, it dies [3]. Adult neurogenesis following specific types of injury, however, still seems possible. The first indication of this was found in studies using rodent stress models. These studies showed that following a series of extremely difficult psycho-social stressors, there was a marked decrease in the emergence of neurological precursor cells inside the adult hippocampus's subgranular layer. Pharmacological therapy was able to restore this reduced cell proliferation [4-5]. Non-human primates have also been shown to benefit from antidepressants in terms of increased neurogenesis and brain progenitor cells [6]. Particular parts of the brain may become permanently dormant or die as a result of these disorders. Nerve impulses and the PNS become less effective over time in NDDs before dying. Although there are therapies available, there are unavoidable adverse effects associated with each one. The intricacy of the brain, side effects, and BBB permeability make clinical research of CNS drugs difficult [7]. The most delicate and complex organ system, the brain, is shielded by the blood-brain barrier. It provides defense against potentially harmful and destructive substances in the bloodstream for the cerebral neurons [8], but it also poses a significant barrier to the delivery of drugs into the central nervous system (CNS). Ninety-five percent of the compounds are not developed into drugs because of the BBB [9]. Recent studies have demonstrated that the blood-brain barrier (BBB) is a dynamic interface that controls the flow of chemicals from the bloodstream into the brain [10]. It is composed of a monolayer of polarised endothelial cells connected by intricate tight junctions, and astrocytes, neurons, and pericytes regulate its function [11].

The blood-brain barrier (BBB) serves as a shield for the brain in a healthy individual, keeping various substances from the bloodstream out of the brain and preserving normal brain function. Because of this, the BBB is only permeable by very small particles. The diameter of the capillaries in the brain can range from 7 to 10 µm [12-13]. Only lipid-soluble, small molecules with a molecular weight of less than 400 da can pass through the blood-brain barrier. The vast majority of macromolecules are unable to cross the brain endothelium [14]. To maintain the lowest possible ocular concentrations, the BBB also regulates the entry of potassium (K+), calcium (Ca2+), and sodium (Na+) ions at synapses. The BBB is responsible for controlling the flow of substances into and out of the brain, maintaining ionic balance, and protecting the brain from substances that can damage it, such as xenobiotics, neurotransmitter systems, and drugs that are part of the systemic circulation [15]. To successfully carry drug over the BBB and into the central nervous system, an appropriate nanocarrier technology must be found. Brain microvascular endothelial cells (BMVECs) and certain other treatment system components (such as neurons, astrocytes, pericytes, and basal lamina) form a tight connection that protects the CNS and ensures its proper functioning. A vast array of pharmaceuticals with different structures and therapeutic purposes can be easily expelled from cells by the ATP-binding cassette (ABC) protein superfamily, which includes most BBB transporters. Our understanding of transporters' functions and contributions to the BBB has improved as a result of P-glycoprotein (P-gp) research [16]. Previous research focussing on BBB permeability has examined the features of secondary messengers that dominate permeability. Extracellular calcium was first shown to be an essential part of tight junction (TJ) control in Ca2+ addition/depletion models [17]. TJ function and assembly quickly adjust to intracellular signaling events that change TJ complexes during pathological and physiological changes.

CNS diseases

Alzheimer's disease (AD)

Alzheimer's disease is the most prevalent chronic progressive neurodegenerative illness in older adults, particularly those over 65. As the disease progresses, symptoms include irreversible cognitive failure, behavioral impairment, and insanity. An estimated 47 million people worldwide are thought to be suffering from madness; of these, about 36 million have made an announcement. It is predicted that this figure will rise by 131 million by the year 2050 [18]. ADaffected individuals experience gradual memory loss, diminished superintendent function, language degradation, and finally pass away from Alzheimer's as a result of severe neuronal loss [19].

Parkinson's disease (PD)

The second most prevalent neurodegenerative disease, Parkinson's disease, is distinguished by motor abnormalities like as bradykinesia, or slowness of movement, severity, and postural insecurity [20]. Ninety to ninety-five percent of Parkinson's disease (PD) cases do not appear to have an inheritable base; on the other hand, five to ten percent of cases are associated with inherited mutations, and fifty percent of cases of early-onset PD are caused by loss of function mutations in the parkin gene, which encodes an E3 ubiquitin ligase [21]. Numerous mechanisms have been identified as critical in the progression of Parkinson's disease (PD), including misfolding and aggregation of α-synuclein, dysfunctional protein concurrence systems, mitochondrial dysfunction, the ubiquitin-proteasome system, the autophagy-lysosome system, and neuroinflammation [22]. Optimizing dopamine levels in the brain is the most popular way to treat Parkinson's disease (PD); yet, neither the disease's course nor the health of the impacted dopaminergic neurons is changed by this approach [23]. Before age 50, Parkinson's disease (PD) rarely manifests, while in older adults, the frequency of complaints peaks at approximately. Bradykinesia-like motor and non-motor disabilities, resting tremors, severity, and postural instability are the hallmarks of Parkinson's disease (PD), a complicated neurological illness. The rudimentary ganglia in the substantia nigra pars compacta (SNc) are the site of a selective and gradual degradation of dopaminergic neurons that contributes to the pathophysiology of Parkinson's disease (PD) and results in the disease's initial symptoms [24].

Ischemic Stroke

A disease known as an ischaemic stroke occurs when there is insufficient blood flow in the brain as a result of cerebral vascular inhibition, which is akin to embolization and thrombosis. Ischaemic stroke is the world's top cause of death and disability, according to reports, with a high rate of morbidity, disability, and mortality. Presently available individual strategies for ischaemic stroke primarily rely on clinical symptoms in addition to brain CT and MRI scans [25]. More than 80% of all strokes are classified as acute ischaemic strokes. These strokes are caused by thrombotic or embolic occlusion of a major cerebral roadway (usually the middle cerebral roadway) or its branches, which results in a sudden or permanent reduction in cerebral blood flow. This sets off a chain reaction of metabolic events that, if not quickly stopped, ultimately results in unselective neuronal cell death [26-27].

Tumor

A large class of primary brain tumors known as gliomas are thought to have originated from glial cells and account for 30% of all brain tumors as well as 80% of primary malignant brain tumors [28]. Many types of primary and secondary (or metastatic) tumors can affect the brain. Globally, the incidence of brain cancer is believed to be 3.5 per 100,000 people, and every day, approximately 100 new cases of brain excrescence are reported. A glioma, which accounts for 60 of all primary brain tumors, is the most prevalent type of aggressive brain malignancy, according to the World Health Organisation classification, which lists approximately 60 different types of primary excrescences. Gliomas can now be diagnosed with them thanks to recent lightning-fast advancements in many imaging modalities [29]. Less than two years is the median survival time for cases diagnosed with glioblastoma multiforme (GBM), the most prevalent and malignant form of these tumors.

Huntington disease

One common autosomal dominant hereditary condition that results from a mutation in the Huntingtin gene is Huntington's Disease (HD), commonly referred to as Huntington's chorea. Though the precise medium causing HD is still unknown, the mutation results in abnormal Huntingtin protein, which is harmful to cells [30]. Huntington's genes, sometimes referred to as complaint-causing genes, produce aberrant Huntington's proteins, which cause neurons to start dying [31-32]. When a person with Huntington's disease reaches adulthood, at approximately 45 years old, their motor and cognitive abilities abruptly deteriorate and their behaviour patterns are significantly altered [33].

Sclerosis and migraine

Neurons develop demyelination and eventually die as a result of the autoimmune inflammatory disease known as multiple sclerosis. By selectively killing oligodendrocytes, which produce myelin, lymphocyte infiltration into the central nervous system (CNS) mediates the demyelination process and sets off autoimmune and inflammatory

reactions [34]. A bilateral or unilateral shifting headache that occurs occasionally is called a migraine. A period of prolonged neuronal inactivity followed by a burst of high neuronal activity that gradually spreads throughout the brain is indicative of cortical spreading depression (CSD), an implicit signal [35].

Neuropathic pain

Neuropathic pain is a persistent pain condition that is usually caused by damage or malfunction of nerve fibers as a result of injury to the central or peripheral nerves. This syndrome occurs frequently throughout the world, is very difficult to treat, and is a sequel to several disorders, including trauma injury and multiple sclerosis [36]. The activation of astrocytes and microglia leads to inappropriate pain signaling, which causes neuronal sensitization after additional nerve injury, however, the exact cell mechanisms underlying this are unknown.

NANOPARTICLES

Paul Ehrlich, the winner of the Nobel Prize, popularised the idea of the "Magic Bullet" in the early 1900s. Ehrlich claimed that certain drugs could "hit a specific target, overcoming several physiological and cellular barriers, increasing the drug bioavailability and decreasing the appearance of the possible side effects." In light of this notion, DDS based on nanotechnology has developed as an alternative method to get past the BBB and achieve brain targeting. Their capacity to bypass the immune system, penetrate the blood-brain barrier, and locate target tissues determines how the DDS will behave. Various nano-delivery technologies have been developed over the past 20 years to boost the low bioavailability of particular drugs and nutraceuticals, minimize peripheral adverse effects, overcome the blood-brain barrier, and increase the therapeutic action of these molecules in the brain [37].

Ideal properties of Nanoparticles for crossing CNS: [38]

- Nontoxic, biodegradable, and biocompatible.
- Tiny particles, between 1 and 100 nm in size.
- A reasonably priced and scalable manufacturing method.
- Compatible with nucleic acids, proteins, peptides, and tiny compounds.
- Stability of the body in vitro and in vivo.
- Steer clear of the reticulo-endothelial system (RES), which lengthens the time blood circulates.
- Targeting the CNS through transcytosis across brain capillary endothelial cells via receptor-mediated interaction.
- Drug alteration (chemical declination/modification, protein denaturation) caused by minimum nanoparticle excipients and formulation stability
- Controlled release qualities and the ability to shield the drug from deterioration.

Mode of action of nanoparticles

A few of the physiochemical characteristics of nanoparticles that allow them to cross brain endothelial tissue are their tiny size, hydrophilicity, surface charge, and ability to target ligands with nanocarriers. The positive charge on the surface of the nanoparticle and the negative charge on the brain's endothelial cells interact due to the existence of electrostatic interactions between the carrier and cells [39]. Because it is linked to the compound's permeability and solubility, the lipophilic nature of the nanomaterials improves their characteristics and quickens the adsorption process. When low-density lipoprotein receptors are present on brain endothelial cells, the nanoparticle is taken up by endocytosis and transcytosis, which is followed by desorption [40].

Owing to this desorption, the particles enter the bloodstream again and discharge the drug that was enclosed in them onto the surface of the blood-brain barrier, where it diffuses throughout the brain's parenchyma. Because human blood capillaries have an average diameter of 6–9 μm and a cell diameter of 20 μm, nanoparticles can readily pass through the endothelial cells of the blood capillary due to their tiny size through transport mechanisms such endocytosis and transcytosis [41]. After being endocytosed, these drug-carrying nanoparticles penetrate deeper into the parenchyma or cell of the brain. Nanoparticles are thought to function through a variety of processes, while their exact mode of drug delivery is still unknown.

A possible explanation is that a general surfactant solubilizes the lipids in the endothelial cell membrane,

facilitating fluidization of the membrane and enhancing permeability across the blood-brain barrier [42]. Another way that nanoparticles might work is by causing toxicity to the brain's blood vessels. Nanoparticles can also cross the BBB by opening the TJs. The enhanced absorption and retention of nanoparticles in the capillary walls and brain-blood capillaries assist processes such as transcytosis and endocytosis through the layer of endothelial cells. This leads to a higher concentration gradient, which should enhance the amount of material that is transported through the endothelial cell layers. However, because the drug being diffused may efflux out due to many transporters, including P-gp, it is not a good route to deliver pharmaceuticals across the blood-brain barrier [43].

Types of nanoparticles delivering drugs to CNS

Drug delivery for central nervous system illnesses can be accomplished with the help of nanotechnology [44]. One benefit of nanoparticles is their ability to pass the blood-brain barrier with a site-specific drug delivery mechanism. Solid-lipid nanoparticles (SLNs), dendrimers, liposomes, micelles, and PNPs are a few examples of the several types of nanoparticles, each having a unique composition and function [45].

LIPOSOMES

Liposomes are little spherical colloidal vesicles of the first generation. These are hydrophilic, and include one or more lipid bilayers at their core, which is why they visually mimic cell membranes and can be employed in drug delivery applications. These are typically divided into three groups based on the size and quantity of bilayers: multilamellar, which ranges from 20 to 100 nm, small unilamellar, which ranges from 10 to 50 nm, and large unilamellar, which ranges from 50 to 1000 nm [46]. Numerous neurological illnesses can be treated with these nanocarriers, as they have demonstrated substantial therapeutic promise. The BBB is easier to traverse for liposomes because of their phospholipid bilayer. Because lipids can safely flow to the peripheral organs and perform noninvasive procedures, liposomes are well known for their biocompatibility.

After circulating in the body normally and unchanged for a short while, RES cells quickly remove normal, unaltered liposomes from circulation. As a result, numerous attempts have been made to create customized, long-circulating liposomes. The successful evasion of RES detection of nanocarrier systems has been seen when polyethylene glycol (PEG) coating of liposomes is applied. Further tinkering with PEG-modified liposomes utilizing ligands such as human insulin receptors, transferrin receptors (TRs), or glial fibrillary acidic protein (GFAP) may enhance the targeted transport of the liposomes to the brain. Transferrin-conjugated liposomes have demonstrated enhanced brain delivery of payloads, including 5-fluorouracil, due to receptor-mediated endocytosis [47].

Immunoliposomes, which can better disperse liposomes inside the brain and are very effective against experimental autoimmune encephalomyelitis, are made by combining prednisolone-loaded liposomes with mAbs that are recognized by cell surface receptors in the targeted tissue. By combining a tyrosine hydroxylase plasmid with a liposome targeted by the TRsMAb, it has been demonstrated that immunoliposomes—a type of nanocarrier system used for the delivery of brain drugs—can also be used in gene therapy to treat Parkinson's disease in rats. EGFR knockdown and enhanced survival in mice with intracranial brain tumor implants have been observed through the delivery of small interfering RNA (siRNA) that targets the EGFR. Utilizing cell-penetrating peptides to change liposomes is another way to increase their ability to cross barriers and increase therapeutic efficacy [48]. When combined with non-specific cell-penetrating peptide (TAT), which has been demonstrated to have high availability across the BBB and specific cell targeting to brain glioma, and the particular ligand transferrin (T7), for example, doxorubicin-encapsulated liposomes may be employed. Nimodipine PR liposomes produce a liposomal structure when bound to water. Since liposomes have certain unique characteristics and a certain structure, they can function as an effective drug delivery mechanism with little to no antibody activation [49].

Solid Lipid Nanoparticles (SLNs)

Triglycerides and fatty acids are two examples of the lipids included in SLNs, which are aqueous colloidal mixes. These dispersed nanoparticles in solution acquire the capacity to solidify upon cooling. Since SLNs exhibit low cytotoxicity, prevent drug alteration, and are physically stable, they are being evaluated for drug delivery to the brain. drugs that are hydrophilic or lipophilic can be encapsulated in SLNs, and because the encapsulated drugs are more stable in SLNs than in PNPs, a protracted release profile spanning months to years is achievable. When compared to PNPs, SLNs prevent leakage and shield the active pharmaceutical ingredient from oxidative, chemical,

and photochemical degradation by immobilizing it inside the formulation, which produces a stable state [50]. Because the lipids are physiologically stable, it has been claimed that the bioavailability of hydrophobic drugs is enhanced when they are formulated as SLNs as opposed to PNP encapsulation.

Solid-lipid nanoparticles (SLNs) are attracting a lot of attention these days as possible novel drug carriers. Many efforts have been undertaken to increase the SLNs' long-term durability and drug-loading capacity [51]. One of these efforts involved combining spatially different lipids or merging solid lipids into liquid lipids to create nanostructured lipid carriers (NLCs).

Studies that contrasted standard SLNs and PEG-modified SLNs containing anticancer drugs like camptothecin and doxorubicin found that the PEG modification of SLNs enhanced their capacity to cross the blood-brain barrier and enhanced the delivery of drugs to the central nervous system [52]. Furthermore, apolipoprotein E, a plasmatic protein that adsorbs onto the surface of SLNs, may facilitate the protein's uptake into the brain. Adhesion to the endothelial cells that comprise the blood-brain barrier would aid in this. The above-discussed method has been used to encapsulate a wide range of pharmaceuticals to achieve target-specific delivery of drugs across the BBB [53]. Stearylamine-based SLNs carrying the antipsychotic drug clozapine have been demonstrated to efficiently deliver the drug into the brain following intravenous and intraduodenal injections. Drug-loaded SLNs include, for example, quercetin-loaded SLNs for Alzheimer's disease treatment and atazanavir-packed SLNs for the treatment of HIV encephalitis. A rat model of amyotrophic lateral sclerosis (ALS) created by vaccination with experimental allergic encephalomyelitis has demonstrated the superior efficacy of riluzole-loaded SLNs over free riluzole.

In terms of Parkinson's disease, neither DA nor L-DOPA have been included in lipid nanoparticles that have demonstrated in vivo effects. On the other hand, DA agonist ropinirole has been encapsulated in lipid formulations that are NLC and SLN. When administered orally, the lipid nanoformulation loaded with ropinirole demonstrated approximately a 2.5-fold improvement over the unmodified drug [54]. Furthermore, topical application of this nanoformulation increased ropinirole concentration by up to three times when compared to the free drug control group. Thus, following its nanoformulation, the drug's bioavailability was improved, leading to a rise in neurotransmitter levels and a fall in lipid peroxidation levels in both oral and topical treatment. Lipid-based NPs may also cause hypersensitivity known as CARPA (complement activation-related pseudo allergy) and unfavorable immune reactions, which compromises their safety and effectiveness when administered to people [55].

Polymeric Nanoparticles (PNP's)

Polymeric nanoparticles are among the first and most effective methods in the field of DDS [56]. After receiving FDA approval in 1974, polylactic glycolic acid (PLGA) has become the biomedical industry's most successful polymer by far. Furthermore, the possibility to employ PLGA microparticles as drug carriers of a broad range of medicinal compounds was made possible by their initial approval in 1989 with Lupron Depot®.

Traditional AD drugs, such as rivastigmine, have been encapsulated in PLGA NPs to improve brain entrance, reduce frequent dosage, and minimize cholinergic side effects. An acetylcholinesterase (AchE) inhibitor that has FDA approval is donepezil. More NPs were able to breach the blood-brain barrier as a result of the surface modification with Tween 80, enabling brain targeting after IV injection. The addition of surfactant to NPs caused the BBB's tight connections to open via an endocytosis or transcytosis mechanism, releasing the drugs inside brain endothelial cells and delivering them to the brain [57]. Furthermore, Tween-80 surface coating suppressed P-glycoprotein and the efflux mechanism, which improved drug transport to the brain through the blood-brain barrier. The results using gamma scintigraphy pictures demonstrated increased brain accumulation of donepezil-loaded NPs, despite accumulation in off-site organs. To boost brain concentration, PEG has been utilized to alter the NPs' surface to give them stealth characteristics and immune system evasion. Galantamine-loaded NPs were made in this manner to treat AD. The potential of this innovative nanoformulation to raise drug concentration in the brain was reported by the intravenous injection of PEG-PLGA NPs combined with ascorbic acid. The commercial drugs as well as other treatments under investigation, like growth factors and neurotrophic factors, have been encapsulated to enhance their biodistribution [58]. This has resulted in higher therapeutic levels of these treatments in the brain and a lower chance of systemic side effects. Despite its potential for treating diseases, NTFs are not yet fully translated to the clinic due to several factors, including their short half-life and limited bioavailability. To get over these drawbacks, a novel therapeutic strategy for AD has been developed: PLGA NPs encapsulating basic

fibroblast growth factor (bFGF). To boost GF brain levels following intranasal treatment, these PLGA-NPs were further conjugated with Solanum tuberosum lectin (STL) and surface-modified with PEG [59].
The most effective therapy for Parkinson's disease (PD) available today is dopaminergic therapy. Although the clinical standard treatment is levodopa, or L-DOPA, a DA prodrug, only 1% of given L-DOPA may enter the brain intact. Furthermore, the short half-life of L-DOPA means that large doses must be administered frequently, which can have several negative consequences, such as dyskinesia or the wearing-off and on-off phenomenon brought on by repeated administration [60]. Drug release control and biodistribution can be altered with NPs-based DDS, minimizing adverse effects and optimizing therapeutic benefits while mitigating these disadvantages.

MAGNETIC PARTICLES

Of the new nanomaterials for targeted therapies, magnetic nanoparticles are one. The nanoparticles' superparamagnetic features, which are dependent on their magnetic properties, make them attractive candidates for stimuli-responsive targeted remedies. Giving the right amount of drug at the right location limits the effectiveness of conventional drug delivery methods. The natural system can be manipulated and acted upon by magnetic particles functionalized with chemical or biological drug molecules using an external magnetic field. For CNS illnesses, when traditional methods are unable to cross the blood-brain barrier, this makes them appropriate for drug delivery [61]. Among the inorganic nanoparticle systems for targeted drug administration that have been studied the most are superparamagnetic iron oxide nanoparticles. Magnetic particles less than 200 nm are ideal for targeted therapies. Improved dispersibility has been observed in magnetic iron oxide nanoparticles functionalized with carboxylic or amino acid groups in recent years. The use of oligosaccharide-coated magnetic iron oxide nanoparticles as a brain tumor target has been investigated [62]. Improved theranostics applications were made possible by the oligosaccharide-coated magnetic particles, which enabled noninvasive magnetic resonance imaging of cancer cells. A possible way to improve the colloidal stability of magnetic particles and potentially enable practical BBB crossing is by polymeric encapsulation [63]. Polymeric coverings also prevent proteins from breaking down the drug and increase its bioavailability. To specifically treat ischaemic stroke, carnosine and dexamethasone were added to magnetic iron oxide nanoparticles (Fe3O4) functionalised with poly(lactic-co-glycolic acid) [64]. Depending on the size, form, surface chemistry, dosage, and mode of administration of the magnetic nanoparticles, brain cells may react differently to them immunologically. While smaller particles might be able to avoid detection, larger particles are recognized by the immune system more easily and trigger a stronger response. Compared to magnetic nanoparticles with a neutral or negative surface charge, those with a positive surface charge may elicit a greater immunological response. Several approaches are used to address immunological responses seen in brain drug delivery with magnetic nanoparticles. Preferably, magnetic nanoparticles should be coated with a biocompatible polymer.

DENDRIMERS

Polymeric macromolecules called dendrimers have hyperbranched network architectures and can be modified in terms of surface functions. Biological molecules (antigens, antibodies, and oligonucleotides) and drug molecules are effectively transported throughout biological systems by dendrimers, which function as nanocarriers. As dendrimers have so many benefits, including pH stability, adjustable solubility, drug-loading capacity, surface functionalization ability, and biocompatibility, they have been extensively studied as nanocarrier technologies [65]. Poly(amidoamine) (PAMAM) is the most studied drug delivery agent for oral administration due to its water solubility and ability to cross epithelial tissue, which enhances the drug's transfer via the paracellular pathway. Dendrimers are classified into several types based on their functionalization moieties: PAMAM, PPI, liquid crystalline, core-shell, chiral, peptide, glycodendrimers, and Radially layered poly(amidoamine-organosilicon) (PAMAMOS). Due to the presence of amine groups, dendrimers have restricted therapeutic applicability [66]. The drug is delivered by dendrimers in two ways: first, through the covalent bonding of the drug being broken down in vivo by available enzymes or by a favorable environment that can break the bonds; second, through the drug being released as a result of changes in the physical environment, such as pH, temperature, etc. In comparison to free doxorubicin, the concentration of doxorubicin in the tumor was shown to be 121.5 times higher after 24 hours in the folate-attached poly-l-lysine dendrimers (doxorubicin hydrochloride) as a potent cancer prevention drug carrier model for pH-dependent drug discharge, target specificity, and antiangiogenic and anticancer perspective.

Analogously, methotrexate (MTX) can be delivered to cancer cells selectively via folate-conjugated polypropylene imine dendrimers (FA-PPI) for use as an anticancer drug carrier and pH-sensitive drug release. Their in vitro investigations on MCF-7 cell lines demonstrated low cytotoxicity, enhanced cell uptake, and prolonged release. Additionally, it should be noted that in contrast to methotrexate (MTX) in its free form, the produced formulations, methotrexate (MTX)-loaded and folic acid-conjugated 5.0G PPI (MTX-FA-PPI), were taken up by the tumor cells preferentially [67].

Micelles

Micelles are vesicles composed of amphiphilic surfactants, which are non-polymeric, or amphiphilic copolymers, which are polymeric, and they have recently caught the interest of scientists due to their potential application in the delivery of drugs to the central nervous system. Micelles remain stable in an aquatic environment because of the hydrophilic coating on the outside [68]. Furthermore, it increases their accumulation in leaky vascular regions and shields them from the reticuloendothelial system (RES) by prolonging their blood circulation. The poloxamer, or pluronic copolymer class, is of particular interest since it has the potential to block drug efflux transporters. Due to its widespread expression on the BBB, the P-gp efflux carrier facilitates drug delivery to the central nervous system.

Several attempts have been made to modify micelles so that a higher concentration of loaded drug can easily cross the BBB on the other side. The binding of polyclonal antibodies to the luminal side BBB receptor in opposition to the brain-specific antigen, 2-glycoprotein, or insulin is one such alteration [69]. Both the neuroleptic activity of the drug haloperidol and the transport of fluorescent dye are markedly increased when these modified micelles are given intravenously to mice after being loaded with either agent. The drug molecule and the targeting moiety are directly conjugated to the amphiphilic region in another form of the micelle technique. For example, transferrin-modified cyclo(Arg-Gly-Asp-d-Phe-Lys) paclitaxel conjugate-loaded micelles found more prolonged retention in glioma tumors in vivo and improved absorption by brain microvascular endothelial cells in vitro, both without significant toxicity [70]. When the lipophilic drug carrier resveratrol was added to PLGA-CS-OA, it was demonstrated to be more stable than polymeric micelles based on data from TGA experiments, cell line contacts, and effect.

NANOGELS

Hydrogel technology has advanced thanks to nanotechnology, which has created smart nanogels with more sophisticated capabilities than bulk three-dimensional cross-linked hydrogels. Hydrogels with a size range of 1–100 nm are known as nanogels [71]. There are still concerns regarding the toxicity and biodegradability of inorganic nanocarriers, and drug burst release problems are associated with polymer particles of poly-(lactic acid-glycolic acid) copolymer (PLGA).

According to studies, the brain's absorption of insulin is improved when nanogels are taken orally. To covalently bind insulin, poly(N-vinylpyrrolidone)-based nanogels were created and evaluated for brain administration via e-beam irradiation. The investigation indicated that when nanogel was administered intravenously, the nasal mucosa did not react immunologically. This study demonstrates the therapeutic potential of nanogels against certain NDs. Strong nasal drug absorption was shown by olanzapine loaded in chitosan-based nanogels [72]. Using intriguing research, a hydrogen bond-enhanced nanogel system with antioxidant and anti-inflammatory capabilities was developed: glycyrrhizic acid−zinc alginate nanogel, or GA-NG. Selective brain accumulation and distribution were demonstrated by this nano-hydrogel. Enhancing stability, this nano-hydrogel system made use of hydrogen bonding sites for tiny molecules that were active. Such investigations validate the promise of nanogels as noninvasive drug delivery systems and sustained release carriers for Parkinson's disease.

Quantum dots

QDs are semiconductor nanocrystals that have a diameter of 2 to 10 nm. The QDs have garnered significant interest in the field of nanodrug because, in contrast to traditional organic dyes, they exhibit emission in the near-infrared (650 nm) range, which is highly desirable for biomedical imagery because of the low tissue absorption and decreased light scattering [73]. QDs are thought to be the most effective for treating CNS diseases because of these characteristics. For the diagonals and brain disease imaging, several conjugated QDs are employed. The BBB is

unaffected by these semiconductors' chemo-electric characteristics or size. The primary element for QD transport over the BBB is their surface. According to Lien et al.'s research, graphene QDs can prevent the accumulation of Aβ1-42 peptides and have numerous therapeutic uses for this issue. There are several ways to make QDs traverse the blood-brain barrier (BBB), and one of the ways they do so is by bonding with certain molecules [74].

Exosomes

Most nucleated eukaryotic and prokaryotic cells release exosomes, which are extracellular vesicles that can function as endogenous nanoparticles. The components of exosomes might comprise proteins, lipids, metabolites, DNA, and RNA, depending on the origin and functional state of the cell. Exosomes are primarily involved in intercellular communication and can control inflammation, autoimmune, and T-cell-mediated immune responses [75]. Nonetheless, native exosomes derived from mesenchymal stem cells (MSCs) continue to be able to support immunological regulation, migration, homing, and neurite remodeling. Current studies have shown that in PD39 and AD40 illness models, engineered MSC-derived exosomes, or MSC-exos moved to particular brain regions that were ill. It was demonstrated during stroke that exosomes generated from dendritic cells (DC) were immunomodulatory and exosomes derived from macrophages were neuroinflammatory. Exosomes can carry drugs into the brain through the blood-brain barrier because of their small size and endogenous characteristics. Naturally occurring exosomes can cross the blood-brain barrier by binding to receptors on brain endothelial cells. Exosomes have been investigated for bringing neurotransmitters (dopamine) over the blood-brain barrier in the hopes of treating Parkinson's disease, based on their interaction with transferrin receptors [76]. In addition to influencing immunological responses, exosomes are involved in cell-to-cell communication. Macrophages and dendritic cells, for instance, are immune cells that produce exosomes, which, depending on what's inside, can either stimulate or dampen immunological responses.

Use of Prodrugs

Prodrugs are more frequently used to deliver drugs that are unable to cross the blood-brain barrier into the brain without damaging the structural barrier. Most of these are used to treat disorders of the neurons [77]. To transfer drugs into the brain, a variety of prodrug systems are employed, including gene-directed enzyme prodrug systems, receptor-mediated prodrug delivery systems, and lipophilic carrier systems. Moreover, pharmacologically active agents are added to prodrugs—which lack or have minimal biological activity—through chemical modification. These prodrugs then undergo an in vivo transformation to release the active drug. Therefore, without ever releasing the drug in its active state, active prodrugs might be able to cross the barrier once and then again [78]. Prodrugs are bio-reversible drug compounds that alter chemically or enzymatically in vivo to liberate the active parent compound. These substances circumvent obstacles to a drug's utility by acting pharmacologically. Prodrugs have the intended pharmacological action after being delivered to the target site. More precisely, the inclusion of lipophilic groups renders medicinal substances or drugs inactive. Using the most prevalent functional groups that could permit drug permeability through any type of structural or physical barrier, these are created.

Peptide Masking

Furthermore, the existence of different barriers is a significant hindrance to the general use of therapies (including Protein/Peptide (P/P) drugs) that target the brain [79]. However, lipophilicity—which can be attained by adding a cholesteryl group that allows the drug to cross the blood-brain barrier—is necessary for P/P permeability to be successful. These could be administered by any non-invasive technique, such as intraventricular delivery. Nonetheless, another helpful method for the safe transportation of drugs is to disguise the drugs by changing their chemical makeup to make them lipid-soluble.

A lipophilic group increases the likelihood of a peptide passing across the blood-brain barrier, but the peptide's basic properties are obscured when it combines with other chemical groups. For this reason, as cholesteryl is lipophilic, it is utilized in place of cholesterol. This kind of masking helps the drug get through the blood-brain barrier by hiding the fact that it is water-soluble. The brain likewise displays a similar pattern of therapeutic peptides being hidden from peptide-degrading enzymes. Larger molecules may not pass through, though, if shorter peptides with a high surface charge attach to receptors on one side only. Nonetheless, the drug may be coupled to a target molecule, which would enable the drug to cross the blood-brain barrier with ease [80]. Peptide masking is

further aided by C-terminal peptide thioesters. These also have an impact on how secondary amines are employed to remove the Fmoc group from peptides and aminolyze them. However, their synthesis is carried out using the backbone amide linker (BAL) approach, which masks the thioester functionality as a trithioortho ester during the process. It would improve the drug's efficacy and delivery. Nevertheless, despite their promise, a large number of peptide and protein drugs (P/P drugs) now on the market are unsuccessful in treating conditions because they cannot be sustained or delivered to the brain. Because they can readily traverse the blood-brain barrier and deliver the drug in pharmacologically meaningful doses, masking molecules with low molecular weights (400–500 Da) are ideal for high accessibility.

Current Approaches and Challenges

Considerable efforts are currently being made to investigate proven nanodrug strategies for the management or treatment of CNS disorders. Even However, many of the advancements are still in the early phases and require more thorough preclinical testing using a variety of animal models. The development of proven nanodrugs to treat CNS disorders in the clinic is hampered by concerns about safety, effectiveness, and nonsupervisory matters. The BBB can be opened non-invasively when applying external stimulation, such as electromagnetic fields or ultrasound, to improve the delivery of drugs to the brain. However, this approach has the potential to cause colourful neurobehavioral disorders or other related negative effects. Systemic blood circulation is typically how the most potent CNS rectifiers access the brain during traditional delivery [81]. Protein-nimbus formation is recognized as a hindrance to the development of single and therapeutic nanoparticles for in vivo procedures. The efficiency of the nanoparticles' targeting can be hampered by serum proteins that collect around them [82]. Recent investigations conducted in vitro have demonstrated that the size of the paralyzed protein nimbus is influenced by the NP face charge. Several research groups have thoroughly examined the impact of various flyspeck packets on the protein list. Thus, prospective, reasonably priced announcement rectifiers may be developed shortly by assessing the efficacy and safety of appropriate NPs through fatal clinical trials.

Nanotechnology may also play a role in improving the efficacy of the neutron prisoner cure and in optimizing the delivery of boron to brain excrescences. The process of initiating nuclear reactions in the presence of free low-energy thermal neutrons and boron-10 is known as boron neutron capture therapy (BNCT). These neutrons are harnessed by boron-10 to produce high linear energy transfer (LET) nascence patches and flinching lithium-7 capitals, which ultimately destroy excrescence cells. At now, the treatment of neutron prisoners involves the use of low molecular weight substances, specifically sodium borocaptate and boronophenylalanine. Promising results have been shown in studies where cells were exposed to boron-containing nanocarriers, such as increased targeting of excrescence cells, decreased toxicity to healthy cells, and high BBB saturation [83].

Limitations and future directions

Nanodrug has recently led to the development of customized drugs as well as intriguing new ways to treat CNS diseases. It is necessary to consider it a successful way of supplying drugs over the BBB [84]. Therapeutic drug carriers have the potential to diffuse across brain tissue, penetrate the blood-brain barrier, and target specific cells via signaling mechanisms.

Nanotechnology-based pharmaceutical delivery systems have been continually investigated and emphasized in the vast majority of nanodrug drugs being utilized to treat CNS diseases. Furthermore, several nanodrugs are presently undergoing research trials; nevertheless, little is known about their transportation and security at this time [85]. Instability within the BBB, oxidative stress, and amino acid breakdown could all be caused by the characteristics and content of nanoparticles [86], increasing their neurotoxic effects on the brain. Drug loading may be restricted by functionalized nanoparticles' large surface area and compact form, which may lead to particle aggregation despite their successful therapeutic localization. The amount of nano drug and the method of pharmaceutical delivery may both contribute to increased neuroinflammation, which can result in oxidative stress, damage to DNA, and allergic reactions. Therefore, it is essential to understand the biodegradability and biocompatibility of nanodrugs. Developing and implementing standardized techniques to assess the toxicity of nanoformulations in both in vitro and in vivo research is indeed critically needed to provide complete information on the toxicity of nanoformulations in humans.

Successful applications of nanodrugs must interact with neurons on a systemic level. Because of the intricate cellular connections and limited anatomical accessibility at the neuronal level, drug transport may be more problematic. It is a major issue to keep the central nervous system's vital functions intact during drug delivery. Several multifunctional nanomaterials have been the subject of research, and the results have shown remarkable challenges that need to be quickly overcome. For example, some of the micromaterials have properties like biological reasonableness, effectiveness, biocompatibility, and toxic effects in the living organism classifications [87]. Among the many challenging issues being worked on are the modification and control of nanotechnology, pharmaceutical cargo packing, drug delivery to the brain, deep brain stimulation (DBS), implantation stimulation, and even brain cell activity. The creation and characterization of nanoparticles appear to be crucial for their use in drug delivery to prevent unintentional harm to healthy cells. Depending on the degree of neurodegeneration a patient experiences, these advancements should make it simpler to develop drugs in the future.

A small number of other nanoformulations, such as organic or inorganic nanocarriers, are also presently being investigated in preclinical research to decrease the incidence of cancer and lengthen life expectancy. The NanoTherm® treatment, which similarly uses ferrofluid made of SPIONS, was invented by a German company by the name of Magforce. The ability of these nanoparticles to kill cancerous cells by radiation and magnetic hyperthermia has been shown [90]. Magnetic-electro nanoparticle-driven brain stimulation is one of the potential indications; this could be a major implanted DBS therapy in the future [88]. This nanosystem may be engineered to produce magnetothermic, magnetoelectric, acoustoelectric, photothermal, and photoelectric transformations, which would cover tissue and cellular brain activities in many locations. The control of such stimulating and excitatory properties can be adjusted based on the requirements of the brain tissue or cellular response.

Janus-based nanotubes (JBNTs), which resemble DNA but may carry a charge and change in size based on the side chains of the structure, are a novel sort of treatment that can transport particles across the blood-brain barrier. These nanotubes become more functional with each side chain or alteration that is added, improving their capacity to target and treat particular conditions [89]. These materials mimic natural collagen to prevent possible immune reactions, but they also self-assemble using DNA-like principles to form a nanotube that is flexible enough to complex with RNAs targeted to a range of different organs. As opposed to comparable carbon nanotubes, JBNTs are more useful due to their capacity to form larger delivery vehicles and a range of distinct shapes based on the drug's chemistry. Since JBNTs are DNA-inspired, they also exhibit improved endosomal escape and avoid many of the harmful side effects linked to existing vehicles, such as polymers, carbon nanotubes, and liposomes.

New therapeutic options for the treatment of neurodegenerative diseases have emerged, including targeted gene modification using gene-editing technologies (TALENs, CRISPR/Cas9) [90]. Implicit corrective solutions have become more prevalent as a result of advancements in nanotechnology to slow the onset of Alzheimer's disease. Hybrid nanodrug—a combination of NPs and EVs—is an efficient direct delivery technique as a result of ongoing research into producing NPs, exosomes, and ligands at a rate that is appropriate and the evolution of circumstances related to cut-hidden technology. Situations involving CSF endothelin-1 are associated with the rigidity of HIV encephalopathy and are enhanced in HIV-1, ischaemic stroke, and subarachnoid hemorrhage.

Conclusion

The number of people with CNS diseases and brain tumours is continuously increasing as a result of the environment's and lifestyle's ongoing decline. Because of these conditions' distinct surroundings, sensitivity to outside substances, and intricate structures, which make it challenging to administer drug through them, the primary treatment problem is the BBB's impermeability. A robust and efficient carrier that could deliver the drugs to the target place effectively and with little to no adverse effects has to be developed. When it comes to treating CNS illnesses, nanoparticles have demonstrated to be powerful and effective carriers when compared to traditional therapy.

As theranostics for neuroprotection, nanoparticles such liposomes, polymeric nanoparticles, dendrimers, and micelles are much sought after. There is a lot of interest in nerve growth factors and nanoformulations for neurological illnesses, but little information is known about their side effects. Nevertheless, nanotechnology has unequivocally shown itself to be a creative and inspiring source of scientific knowledge, allowing for the accurate

and simple administration of drugs to the central nervous system. There is an urgent need to investigate novel therapeutic options with promising outcomes due to the increasing number of brain illnesses and the growing population. Utilising nanotechnology in neuroscience could solve unfulfilled clinical needs and offer better results to patients. Pharmacological delivery to a specific target and sustained drug release may be regulated via a new wave of nanodrug. It is predicted that the existing accepted technique of pharmaceutical distribution may be greatly outperformed by the nanotechnology-based delivery system, which might also yield significantly more productive customised drugs.

References

1. Srikanth M, Kessler JA. Nanotechnology-novel therapeutics for CNS disorders. Nat Rev Neurol. (2012) 24;8(6):307-18.
2. Naz, Falaq, Siddique, Yasir.Human Brain Disorders: A Review.The Open Biology Journal.September 2020;8(1):6- 21.
3. Shakeri S, Ashrafizadeh M, Zarrabi A, Roghanian R, Afshar EG, Pardakhty A, Mohammadinejad R, Kumar A, Thakur VK. Multifunctional Polymeric Nanoplatforms for Brain disease diagnosis, Therapy and Theranostics. Biodrugs. (2020);8(1):13.1-29
4. Abdur Rauf Khan, Xiaoye Yang, Manfei Fu, Guangxi Zhai, Recent progress of drug nanoformulations targeting to brain. Corel (2018) 291:37-64.
5. Vlieghe P, Khrestchatisky M. Medicinal chemistry-based approaches and nanotechnology-based systems to improve CNS drug targeting and delivery. Med Res Rev. (2013) 33(3):457-516
6. DiNunzio JC, Williams RO 3rd. CNS disorders--current treatment options and the prospects for advanced therapies. Drug Dev Ind Pharm. (2008) ;34(11):1141-67.
7. Ekhator C, Qureshi MQ, Zuberi AW, Hussain M, Sangroula N, Yerra S, Devi M, Naseem MA, Bellegarde SB, Pendyala PR. Advances and Opportunities in Nanoparticle Drug Delivery for Central Nervous System Disorders: A Review of Current Advances. Cureus. (2023) 15(8): e44302.
8. Gao Huile, Progress and perspectives on targeting nanoparticles for brain drug delivery, Acta Pharmaceutica Sinica B, (2016) 6(4) 268-286.
9. Yetisgin AA, Cetinel S, Zuvin M, Kosar A, Kutlu O. Therapeutic Nanoparticles and Their Targeted Delivery Applications. Molecules. (2020);25(9):2193.
10. Carvalho M.R., Reis R.L., Oliveira J.M. Dendrimer nanoparticles for colorectal cancer applications. J. Mater. Chem. B, (2020); 8(6); 1128-1138.
11. Wang M, Thanou M. Targeting nanoparticles to cancer. Pharmacol Res. (2010);62(2):90-9.
12. Davis, M., Chen, Z. & Shin, D. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nat Rev Drug Discov (2008) 7, 771–782.
13. Cui-Tao Lu, Ying-Zheng Zhao, Ho Lun Wong, Jun Cai, Lei Peng & Xin-Qiao Tian Current approaches to enhance CNS delivery of drugs across the brain barriers, International Journal of Nanodrug, (2014), 2241-2257,
14. Aryal M, Arvanitis CD, Alexander PM, McDannold N. Ultrasound-mediated blood-brain barrier disruption for targeted drug delivery in the central nervous system. Adv Drug Deliv Rev. (2014); 72:94-109.
15. Abdul Razzak R, Florence GJ, Gunn-Moore FJ. Approaches to CNS Drug Delivery with a Focus on TransporterMediated Transcytosis. Int J Mol Sci. (2019);20(12):3108.
16. Pavan B, Dalpiaz A, Ciliberti N, Biondi C, Manfredini S, Vertuani S. Progress in drug delivery to the central nervous system by the prodrug approach. Molecules. (2008);13(5):1035-65.
17. McCartan R, Khorkova O, Volmar CH, Wahlestedt C. Nucleic acid-based therapeutics for the treatment of central nervous system disorders. Front Genet. (2023); 14:1250276.
18. Wu M, Huang S. Magnetic nanoparticles in cancer diagnosis, drug delivery and treatment. Mol Clin Oncol. (2017);7(5):738-746.
19. M. Azarmi, H. Maleki, N. Nikkam, H. Malekinejad, Transcellular brain drug delivery: A review on recent advancements, International Journal of Pharmaceutics (2020);586:119582.

20. Stockwell J, Abdi N, Lu X, Maheshwari O, Taghibiglou C. Novel central nervous system drug delivery systems. Chem Biol Drug Des. (2014);83(5):507-20.
21. Dong X. Current Strategies for Brain Drug Delivery. Theranostics. (2018);8(6):1481-1493.
22. Hanif S, Muhammad P, Chesworth R, Rehman FU, Qian RJ, Zheng M, Shi BY. Nanodrug-based immunotherapy for central nervous system disorders. Acta Pharmacol Sin. (2020);41(7):936-953.
23. Pk, Jain & Pk, Tiwari & Pushpendra, Kumar & Jain, Pushpendra. Novel Drug Delivery System for Treating Neuropsychological Disorder. International Journal of All Research Education & Scientific Methods. (2023) 11. 2455-6211.
24. Manimaran V, Nivetha RP, Tamilanban T, Narayanan J, Vetriselvan S, Fuloria NK, Chinni SV, Sekar M, Fuloria S, Wong LS, Biswas A, Ramachawolran G, Selvaraj S. Nanogels as novel drug nanocarriers for CNS drug delivery. Front Mol Biosci.(2023);10:1232109.
25. Saeedi M, Eslamifar M, Khezri K, Dizaj SM. Applications of nanotechnology in drug delivery to the central nervous system. Biomed Pharmacother.(2019);111:666-675.
26. Rodà F, Caraffi R, Picciolini S, Tosi G, Vandelli MA, Ruozi B, Bedoni M, Ottonelli I, Duskey JT. Recent Advances on Surface-Modified GBM Targeted Nanoparticles: Targeting Strategies and Surface Characterization. Int J Mol Sci. (2023);24(3):2496.
27. Hossain S, Akaike T, Chowdhury EH. Current approaches for drug delivery to central nervous system. Curr Drug Deliv. (2010);7(5):389-97.
28. Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: a review. J Pharm Pharm Sci. (2003);6(2):252-73
29. uo ZH, Khattak S, Rauf MA, Ansari MA, Alomary MN, Razak S, Yang CY, Wu DD, Ji XY. Role of NanodrugBased Therapeutics in the Treatment of CNS Disorders. Molecules. (2023);28(3):1283. (1-38).
30. Wong HL, Wu XY, Bendayan R. Nanotechnological advances for the delivery of CNS therapeutics. Adv Drug Deliv Rev. (2012);64(7):686-700.
31. de Boer AG, Gaillard PJ. Drug targeting to the brain. Annu Rev Pharmacol Toxicol. (2007); 47:323-55.
32. Pathan SA, Iqbal Z, Zaidi SM, Talegaonkar S, Vohra D, Jain GK, Azeem A, Jain N, Lalani JR, Khar RK, Ahmad FJ. CNS drug delivery systems: novel approaches. Recent Pat Drug Deliv Formul. (2009);3(1):71-89.
33. Pajouhesh H, Lenz GR. Medicinal chemical properties of successful central nervous system drugs. NeuroRx. (2005);2(4):541-53
34. Strazielle N, Ghersi-Egea JF. Potential Pathways for CNS Drug Delivery Across the Blood-Cerebrospinal Fluid Barrier. Curr Pharm Des. (2016);22(35):5463-5476.
35. Tiwari SB, Amiji MM. A review of nanocarrier-based CNS delivery systems. Curr Drug Deliv. (2006);3(2):219-32.
36. Zhang X, Zhou J, Gu Z, Zhang H, Gong Q, Luo K, Advances in nanodrugs for diagnosis of central nervous system disorders, Biomaterials (2020); 269:120492.
37. Cardoso AM, Guedes JR, Cardoso AL, Morais C, Cunha P, Viegas AT, Costa R, Jurado A, Pedroso de Lima MC. Recent Trends in Nanotechnology Toward CNS Diseases: Lipid-Based Nanoparticles and Exosomes for Targeted Therapeutic Delivery. Int Rev Neurobiol. (2016); 130:1-40.
38. Rabiee, Navid; Ahmadi, Sepideh; Afshari, Ronak; Khalaji, Samira; Rabiee, Mohammad; Bagherzadeh, Mojtaba; Fatahi, Yousef; Dinarvand, Rassoul; Tahriri, Mohammadreza; Tayebi, Lobat; Hamblin, Michael R.; Webster, Thomas J. Polymeric Nanoparticles for Nasal Drug Delivery to the Brain: Relevance to Alzheimer's Disease.Advanced Therapeutics, (2020); 4(3):10. (1-42)
39. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. Int J Mol Sci. (2022);23(3):1851.
40. Gao H, Pang Z, Jiang X. Targeted delivery of nano-therapeutics for major disorders of the central nervous system. Pharm Res. (2013);30(10):2485-98.
41. Sim TM, Tarini D, Dheen ST, Bay BH, Srinivasan DK. Nanoparticle-Based Technology Approaches to the Management of Neurological Disorders. Int J Mol Sci. (2020);21(17):6070.

42. Ding Z, Fan X, Zhang Y, Yao M, Wang G, Dong Y, Liu J, Song W. The glymphatic system: a new perspective on brain diseases. Front Aging Neurosci. (2023); 15:1179988.
43. F. Leyan,Wang Heping,Xue Xue.Recent Progress of Nanodrug in the Treatment of Central Nervous System Diseases.Adv. Therap. (2020); 3(5):1900159.
44. Khan, Safir & Khan, Muhammad Imran & Khan, Munir & Khan, Noor & Bungau, Simona & Hassan, Syed. Applications of Extracellular Vesicles in Nervous System Disorders: An Overview of Recent Advances. Bioengineering. (2023);10(1): 51.
45. Dilnawaz F, Sahoo SK. Therapeutic approaches of magnetic nanoparticles for the central nervous system. Drug Discov Today. (2015);20(10):1256-64.
46. Mukherjee, Sudip & Madamsetty, Vijay Sagar & Bhattacharya, Dwaipayan & Paul, Manash & Mukherjee, Anubhab. Recent Advancements of Nanodrug in Neurodegenerative Disorders Theranostics. Advanced Functional Materials. (2020);30(35): 2003054.
47. Kanwar JR, Sun X, Punj V, Sriramoju B, Mohan RR, Zhou SF, Chauhan A, Kanwar RK. Nanoparticles in the treatment and diagnosis of neurological disorders: untamed dragon with firepower to heal. Nanodrug. (2012);8(4):399-414.
48. Fonseca-Santos B, Gremião MP, Chorilli M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. Int J Nanodrug. (2015); 10:4981-5003.
49. Mohammad Shoaib Shaikh Hamid, Pooja R. Hatwar, Ravindrakumar L. Bakal and Nitin B. Kohale. A comprehensive review on Liposomes: As a novel drug delivery system. GSC Biological and Pharmaceutical Sciences, 2024;27(01), 199-210.
50. Esraa Ghazy, Abbas Rahdar, Mahmood Barani, George Z. Kyzas, Nanomaterials for Parkinson disease: Recent progress, Journal of Molecular Structure (2020);1231:129698
51. Vashist A, Manickam P, Raymond AD, Arias AY, Kolishetti N, Vashist A, Arias E, Nair M. Recent Advances in Nanotherapeutics for Neurological Disorders. ACS Appl Bio Mater. (2023);6(7):2614-2621.
52. Patel MM, Patel BM. Crossing the Blood-Brain Barrier: Recent Advances in Drug Delivery to the Brain. CNS Drugs. (2017);31(2):109-133.
53. Nguyen TT, Dung Nguyen TT, Vo TK, Tran NM, Nguyen MK, Van Vo T, Van Vo G. Nanotechnology-based drug delivery for central nervous system disorders. Biomed Pharmacother. (2021); 143:112117.
54. Patel T, Zhou J, Piepmeier JM, Saltzman WM. Polymeric nanoparticles for drug delivery to the central nervous system. Adv Drug Deliv Rev. (2012);64(7):701-5.
55. Patel MM, Goyal BR, Bhadada SV, Bhatt JS, Amin AF. Getting into the brain: approaches to enhance brain drug delivery. CNS Drugs. (2009);23(1):35-58.
56. Parashar, A. K., and R. K. Nema. “A Review on Novel Techniques for Drug Delivery to the Brain”. Current Research in Pharmaceutical Sciences. (2012);2(3):134-141.
57. Xu L, Zhang H, Wu Y. Dendrimer advances for the central nervous system delivery of therapeutics. ACS Chem Neurosci. (2014);5(1):2-13.
58. Kaushik, Ajeet, Jayant, Rahul Dev, Bhardwaj, Vinay,Nair, Madhavan, Personalized nanodrug for CNS diseases.Drug Discovery Today.(2018);23(5):1007-1015.
59. Khatoon, Rizwana & Alam, Md Aftab & Sharma, Pramod. Current approaches and prospective drug targeting to brain. Journal of Drug Delivery Science and Technology. (2020); 61:102098.
60. Krol S. Challenges in drug delivery to the brain: nature is against us. J Control Release. (2012);164(2):145-55.
61. Karthivashan G, Ganesan P, Park SY, Kim JS, Choi DK. Therapeutic strategies, and nano-drug delivery applications in management of ageing Alzheimer's disease. Drug Deliv. (2018);25(1):307-320.
62. Caffo, Maria & Raudino, Giuseppe & Caruso, Gerardo. Nanotechnology and Brain Tumors Drug Delivery. Recent Patents on Nanodrug. (2013); 3:26-36.
63. Nguyen TT, Dung Nguyen TT, Vo TK, Tran NM, Nguyen MK, Van Vo T, Van Vo G. Nanotechnology-based drug delivery for central nervous system disorders. Biomed Pharmacother. (2021); 143:112117.
64. Mendonça MCP, Kont A, Aburto MR, Cryan JF, O'Driscoll CM. Advances in the Design of (Nano)Formulations for Delivery of Antisense Oligonucleotides and Small Interfering RNA: Focus on the Central Nervous System. Mol Pharm. (2021);18(4):1491-1506.

65. Woon CK, Hui WK, Abas R, Haron MH, Das S, Lin TS. Natural Product-based Nanodrug: Recent Advances and Issues for the Treatment of Alzheimer's Disease. Curr Neuropharmacol. (2022);20(8):1498-1518.
66. Ahmad Ainurofiq, Aji Prasetya, Bingah Ginanjar Rahayu, Muhammad Syayiq Al Qadri, Myrat Kovusov, Ophira Evangelista Putri Laksono.Recent developments in brain-targeted drug delivery systems via the intranasal route.FARMAKOTERAPIA.(2022);78 (12): 695–708.
67. Zhou L, Kodidela S, Godse S, Thomas-Gooch S, Kumar A, Raji B, Zhi K, Kochat H, Kumar S. Targeted Drug Delivery to the Central Nervous System Using Extracellular Vesicles. Pharmaceuticals (Basel). (2022);15(3):358.
68. Arnerić s P. Kern V.D. Stephenson D.T. Regulatory-accepted drug development tools are needed to accelerate innovative CNS disease treatments.Translational Drug in CNS Drug Development, (2018);151:291-306.
69. Naqvi S, Panghal A, Flora SJS. Nanotechnology: A Promising Approach for Delivery of Neuroprotective Drugs. Front Neurosci. (2020); 14:494.
70. Won S, A. J, Song H, Im S, You G, Lee S, Koo KI, Hwang CH. Transnasal targeted delivery of therapeutics in central nervous system diseases: a narrative review. Front Neurosci. (2023); 17:1137096. (1-16)
71. Agrawal M, Ajazuddin, Tripathi DK, Saraf S, Saraf S, Antimisiaris SG, et al. Recent advancements in liposomes targeting strategies to cross blood-brain barrier (BBB) for the treatment of Alzheimer's disease. J Control Release. 2017;260:61–77.
72. Dai H, Navath RS, Balakrishnan B, Guru BR, Mishra MK, Romero R, et al. Intrinsic targeting of inflammatory cells in the brain by polyamidoamine dendrimers upon subarachnoid administration. 2010;5(9):1317–29. 102217/nnm1089.
73. Qiu J, Hameau A, Shi X, Mignani S, Majoral JP, Caminade AM. Fluorescent phosphorus dendrimers: Towards material and biological applications. ChemPlusChem. 2019;84(8):1070–80.
74. Flor R, Robertson J, Shevchenko RV, Alavijeh M, Bickerton S, Fahmy T, et al. Multiple sclerosis: LIFNano-CD4 for trojan horse delivery of the neuro-protective biologic "LIF" into the brain: Preclinical proof of concept. Frontiers in Medical Technology. 2021;0:5.
75. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nat Rev Dis Primers. 2017;3(1):1–19.
76. Chia R, Chiò A, Traynor BJ. Novel genes associated with amyotrophic lateral sclerosis: Diagnostic and clinical implications. Lancet Neurol. 2018;17(1):94–102.
77. Niccolini B, Palmieri V, De Spirito M, Papi M. Opportunities offered by graphene nanoparticles for microRNAs delivery for amyotrophic lateral sclerosis treatment. Materials. 20222021;15(1):126.
78. Ediriweera GR, Chen L, Yerbury JJ, Thurecht KJ, Vine KL. Non-viral vector-mediated gene therapy for ALS: Challenges and future perspectives. Mol Pharm. 2021;18(6):2142–60. 10.1021/acs.molpharmaceut.1c00297.
79. Kecel-Gunduz S, Budama-Kilinc Y, Cakir-Koc R, Zorlu T, Bicak B, Kokcu Y, et al. In silico analysis of sulpiride, synthesis, characterization and in vitro studies of its nanoparticle for the treatment of schizophrenia. Curr Comput Aided Drug Des. 2019;16(2):104–21.
80. Kumaran Menon P, Fior Muresanu D, Sharma A, Mossler H, Shanker Sharma H. Cerebrolysin, a mixture of neurotrophic factors induces marked neuroprotection in spinal cord injury following intoxication of engineered nanoparticles from metals. CNS Neurol Disord Drug Targets. 2012;11(1):40–9.
81. Sharma HS, Sharma A. Nanoparticles aggravate heat stress induced cognitive deficits, blood–brain barrier disruption, edema formation and brain pathology. Prog Brain Res. 2007;162:245–73.
82. Lombardo D, Kiselev MA, Caccamo MT. Smart nanoparticles for drug delivery application: Development of versatile nanocarrier platforms in biotechnology and nanodrug. J Nanomater. 2019;2019:1–26,
83. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101–24.
84. [143] Spuch C, Saida O, Navarro C. Advances in the treatment of neurodegenerative disorders employing nanoparticles. Recent Pat Drug Deliv. 2012;6:2–18,

85. Dinda SC, Pattnaik G. Nanobiotechnology-based drug delivery in brain targeting. Curr Pharm Biotechnol. 2013;14(15):1264–74.
86. Sharma HS, Ali SF, Tian ZR, Hussain SM, Schlager JJ, Sjöquist PO, et al. Chronic treatment with nanoparticles exacerbate hyperthermia induced blood-brain barrier breakdown, cognitive dysfunction and brain pathology in the rat. Neuroprotective effects of nanowired-antioxidant compound H-290/51. J Nanosci Nanotechnol. 2009;9(8):5073–90.
87. Vega-Villa KR, Takemoto JK, Yáñez JA, Remsberg CM, Forrest ML, Davies NM. Clinical toxicities of nanocarrier systems. Adv Drug Deliv Rev. 2008;60(8):929–38.
88. Daima HK, Selvakannan PR, Kandjani AE, Shukla R, Bhargava SK, Bansal V. Synergistic influence of polyoxometalate surface corona towards enhancing the antibacterial performance of tyrosine-capped Ag nanoparticles. Nanoscale. 2013;6(2):758–65.
89. Kumar R, Aadil KR, Mondal K, Mishra YK, Oupicky D, Ramakrishna S, et al. Neurodegenerative disorders management: State-of-art and prospects of nano-biotechnology. Crit Rev Biotechnol. 2021;42:1180–212.
90. Gonzalez-Valdivieso J, Girotti A, Schneider J, Arias FJ. Advanced nanodrug and cancer: Challenges and opportunities in clinical translation. Int J Pharm. 2021;599:120438.