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Advance and opportunities in nanoparticle drug delivery for central nervous system disorders: A review of current advances

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Abstract

Nanoparticles drug delivery systems have emerged as a cutting-edge approach in treating central nervous system disorders. This review discusses the advancements and opportunities in utilizing nanoparticles for targeted drug delivery to the brain, focusing on their potential to enhance efficacy, reduce side effects, and improve patient outcomes. Lipid-based nanocarriers like liposomes, solid lipid nanoparticles (SLNs) and micelles are widely used in neurological conditions. The growing demand for innovative drug delivery methods for treating neurodegenerative disorders, such as Parkinson's and Alzheimer's are largely due to potential therapy failures in the blood brain barrier and P-glycoproteins which cause progressive loss of brain function. Nanotechnology advancements can help overcome these limitations by improving the delivery of active medicine campaigns and creating nanomaterials that improve active drug delivery.

Keywords: Alzheimer's disease (AD); Parkinson's disease (PD); Central nervous system (CNS); Blood brain barrier; Nanotechnology

1. Introduction

Nanotechnology offers a potential solution to challenges in treating CNS disorders, such as passing through the blood-brain barrier and enduring cerebrospinal fluid flow. It allows for the engineering of nanoscale materials with functional organization less than 100 nm, allowing them to interact with biological substrates at a molecular level, enabling unprecedented changes in biological systems. [01]. The brain is the command center of the Central Nervous System (CNS) made up of a large mass of nerve cells, protected in the skull [02]. Central nervous system (CNS) diseases are among the most common and complex conditions known in humans [03]. Neurological diseases similar as Alzheimer's complaint, Parkinson's complaint, epilepsy, schizophrenia, traumatic brain injury, brain stroke, ischemia, lysosomal storehouse complaint, anxiety, depression, and multiple sclerosis are major CNS diseases. Alzheimer's complaint involves deposit of Aβ shrine in brain microvasculature and accumulation in the lymphatic cleaning system. Neurological diseases are prevailing in America with further than 100 million American people passing central nervous system (CNS) conditions similar as Alzheimer's complaint and Parkinson's complaint [04]. According to the World Health Organization (WHO), the burden of brain diseases constitutes – 38% of the total burden of all conditions (data grounded on disability acclimated lifetimes), compared to 12.7% for cancer and 11.8% for cardiovascular conditions, and about 1.5 billion people worldwide suffer from CNS diseases [05]. Mainly rarer new drug approvals for CNS diseases compared to other treatment areas are due to several factors including the extended development times, increased medicine development costs, advanced threat of clinical failure and a deficient understanding of both complaint biology and conditions for delivery to the CNS [06].

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The treatment of central nervous system (CNS) diseases poses significant challenges due to the blood- brain barrier (BBB), which restricts the passage of utmost remedial agents from systemic rotation to the brain. Over the times, nanoparticle (NP) grounded medicine delivery systems have surfaced as promising results to overcome these challenges and ameliorate the efficacity of CNS complaint treatments. Nanoparticles offer unique advantages, similar as enhanced medicine stability, prolonged rotation time, and the capability to synopsize a wide range of remedial agents. This narrative review provides an overview of the current advances, challenges, and openings in nanoparticle medicine delivery for CNS diseases [07]. Various kinds of nanoparticle (NP) grounded medicine delivery systems have been constructed using arising new nanomaterials. These nanoparticles include liposomes, dendrimers, micelles, polymer nanoparticles and inorganic nanoparticles which can carry remedial medicines or imaging examinations and deliver them to target point [08]. Nanomedicine is an arising approach for the perpetration of nanotechnological systems in complaint opinion and remedy. This branch of nanotechnology can be classified in two main orders nanodevices and nanomaterials [09]. The use of nanoparticles as drug carriers in oncology began in 1986, when it was noted that nanoparticles showed a tendency to accumulate in tumor tissues [10]. Nanoparticle tumor accumulation is supposed to be possible due to the largely passable blood vessels of the tumors as a result speedy and defected angiogenesis. In addition, tumors are characterized by dysfunctional lymphatic drainage that helps the retention of nanoparticles in tumor long enough to allow original nanoparticle decomposition and release of the medicine in the vicinity of tumor cells. The miracle has been used extensively to explain the effectiveness of nanoparticle and macromolecular medicine accumulation in tumors [11]. Nanoparticle rectifiers are generally patches comprised of remedial realities, similar as small- patch medicines, peptides, proteins and nucleic acids and factors that assemble with the remedial realities, similar as lipids and polymers to form nanoparticles [12]. The BBB consists of the tight junctions (TJs) of capillary endothelial cells on one side and the bottom processes of astrocytes on the other side, whereas the Blood cerebrospinal fluid barrier (BCSFB) is formed by the TJs of choroid supersystem cells girding the microvascular endothelium with intracellular gap and fenestration [13]. The BBB typically protects the brain from poisons and helps maintain the delicate homeostasis of the neuronal medium. Even, it also excludes 98% of small- patch medicines and roughly 100% of large-patch neurotherapeutics from brain parenchyma [14]. The BBB is considered as the primary contributor to the brain's strict permeability due to its larger face area and its high-speed blood flow rate in comparison to Blood cerebrospinal fluid barrier [15]. Cerebrospinal fluid (CSF), which is circulated throughout the subarachnoid space around the brain, is separated from the blood by the BCSFB. This barrier, which restricts paracellular flow, is made up of epithelial cells joined at the apices by tight junctions and is situated near the choroid plexus. The presence of microvilli increases the CSF-facing surface of the epithelial cells that discharge CSF into the ventricles. [16]. CNS diseases comprise conditions with different etiologies ranging from neurodegenerative conditions and internal health diseases to epilepsy and stroke. Despite recent advancements in pharmacology and neuroscience, the therapeutic options for numerous CNS diseases remain limited [17]. Glamorous nanoparticles (MNPs) are a kind of intelligent nanomagnetic material with small flyspeck size, large specific face area, glamorous response and superparamagnetism [18].

Apart from the several routes of administration that encounter the BBB on their path to the central nervous system, it is also important to discuss the intranasal route of administration that has the capacity to circumvent the BBB. Intranasal administration has drawn more interest in recent years as a possible noninvasive method of CNS medication delivery. Aside from a few restrictions that call for low dosages and non-irritating medication compositions, it is regarded as an exceptional method of CNS drug administration since it can cross the blood-cerebrospinal fluid barrier and blood-brain barrier, giving it instant access to the brain. [19]. A major challenge in the remedial treatment of the CNS is the delivery of remedial agents to the target point in the CNS, while having minimum goods on other tissue within the body [20]. The number of elderly people and patients with CNS problems is rising, which means that the worldwide drug development market for brain diseases must expand quickly over the next 20 years. In contrast to other therapeutic domains, medication development for brain illnesses has the lowest success rates. Creating CNS medications often takes much longer than developing non-CNS therapies. [21]. Preventing the course of the disease and treating the symptoms and pathology after a late-stage diagnosis are the main challenges in this area of study. A novel era of therapeutic techniques has emerged because of these challenges. [22].

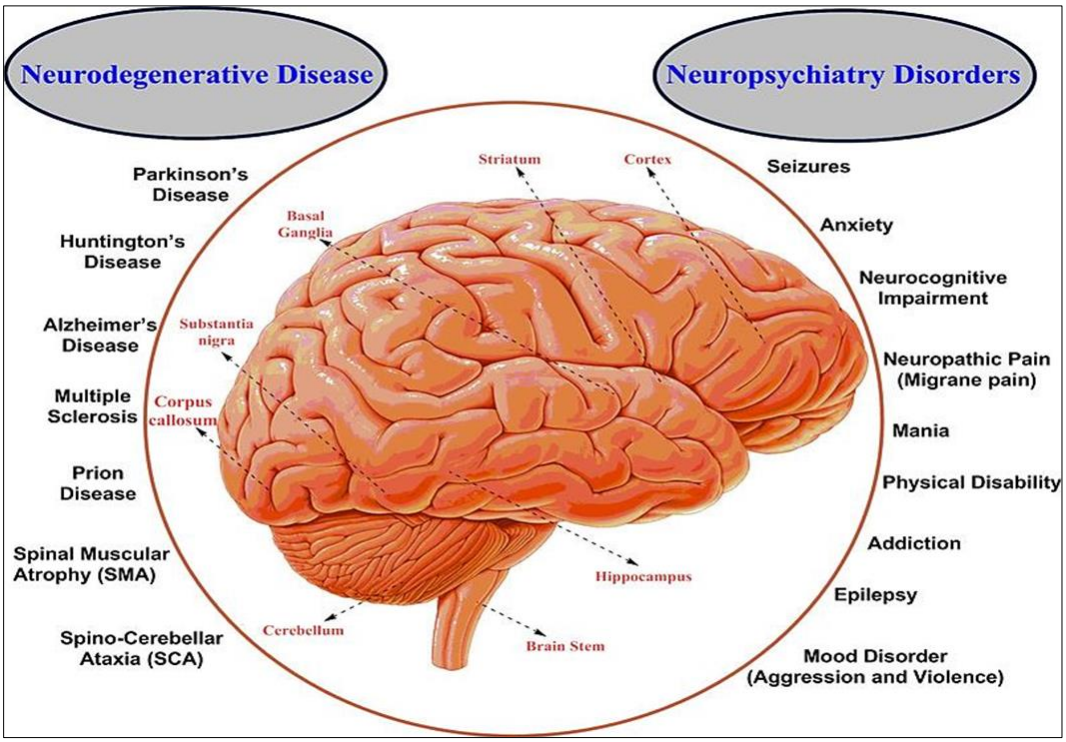


Figure 1 Major human neurodegenerative diseases and neuropsychiatry disorders [02]

1.1. Brain for drug delivery

Different Walls, similar as the BBB, Blood-Cerebrospinal Fluid Barrier (BCB), and Blood- Excrescence barrier, help medicines from reaching the central nervous system (CNS) through the cardiovascular system [23].

1.2. Blood Brain Barrier

The blood- brain barrier (BBB) was first discovered in 1885 by Paul Ehrlich. The BBB plays a pivotal part in guarding the brain from dangerous stimulants, contagious agents and poisons thereby maintaining homeostasis [24]. Mortal brain is the most sensitive and complex organ in the body, which is defended by a membrane called BBB. This border is well suited for guarding the brain neurons against the dangerous and poisonous agents that live in blood. It also affects medicine prolixity to brain towel [25]. The BBB is a rigorously picky cellular barrier located between the blood cube and the brain. On the one hand, it regulates the permeability of small particles and ions to ensure brain nutrition and an applicable neuronal function; alternatively, it prevents unwanted cells and substances from entering the brain [26]. Although the human brain has a large surface area, the brain blood vessel endothelium's total intracellular volume is only 5 ml in the human brain and 1 µl in the rat brain. This indicates that the BBB is extremely thin. The brain's capillary endothelial cells are about 200 and 300 nm thick. Among all biological membranes, this extremely thin cellular barrier has some of the most constrictive permeability characteristics [27]. Thus, the remedial value of numerous promising medicines is lowered, and cerebral conditions have proved to be most refractory to remedial interventions. Given the frequence of brain conditions alone, this is a considerable problem. Virtually all medicines presently used for diseases of the brain are lipid-answerable and can readily cross the BBB following oral administration [28]. During neuro inflammation of the CNS, the brain uses microglia and pericytes as antigen- presenting cells (APCs), which frequently triggers neurological diseases [29].

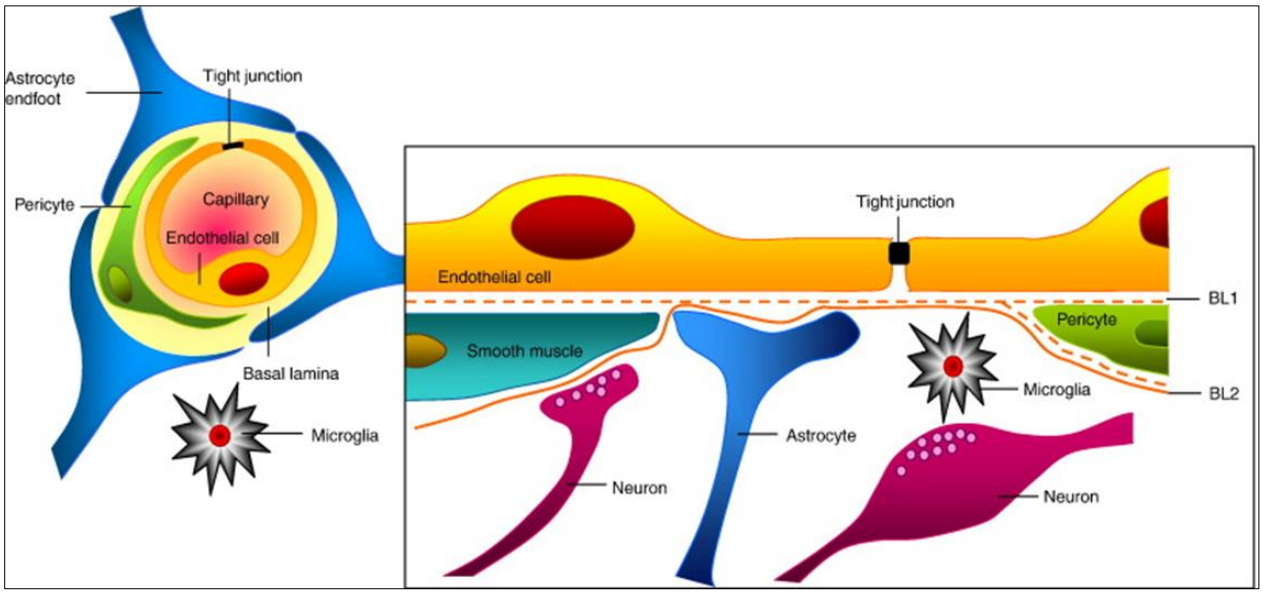


Figure 2 BBBs structure and composition [29]

The most considerably characterized transporter protein at the BBB is P-glycoprotein. This glycoprotein along with certain Multidrug Resistance-associated Proteins isoforms and BCRP are expressed at the luminal membrane of the brain capillary and serve as efflux pumps to extrude xenobiotics from the brain towel back into the rotation. Therefore, they can significantly limit and help entry of substrates into the brain parenchyma [30]. The general permeability of the blood – spinal cord barrier is advanced than that of the BBB [05]. The current knowledge is that the BBB is positioned at the interface of blood and brain and its primary function is to maintain the homeostasis of the brain. Furthermore, the BBB is not invariant throughout the brain because the capillaries in the circumventricular organs (CVOs) are fenestrated [31]. The presence of many endocytic vesicles in the CNS capillaries further removes a transcellular route for free prolixity of substances into the interstitial [32]. The CNS is made to be quite picky about what is permitted in it because it is extremely sensitive to various compounds in the blood as well as drugs [33]. Pericytes, astrocytes, and BECs can freely tone-assemble into ball-shaped cellular summations when deprived of any frame accoutrements. The microfluidic systems go physiologic shear stress to BECs that further produce a laminar flow via a computer-controlled pumping medium [22]. The BBB is extremely effective at widely regulating the terrain within the CNS, but the same physiological characteristic also prevents delivery of therapeutic composites into the CNS [20]. The BBB is the main problem in the treatment of CNS diseases. Therefore, prostrating this barrier is the most critical area of exploration for CNS disease therapy [03].

1.3. Blood Cerebrospinal Fluid Barrier

The alternate barrier that a systemically administered drug difficulties before entering the CNS is known as the blood-cerebrospinal fluid Barrier (BCB) [28]. This barricade is composed of arachnoid and choroidal epithelial cells. Vessel-derived CSF and subarachnoidal CSF are separated by these cells. The choroid plexus (CP), conforming of choroidal epithelial cells, is the main element of the blood- cerebrospinal fluid barrier (BCSFB) [24]. This is set up in the largely vascularized stroma with connective kerchief and choroidal epithelial cells that makes up the choroid's plexus epithelium [23]. These junctions form a functional barrier that restricts the movement of molecules and ions. The main function of the choroid plexus epithelial cells is to cache and maintain the homeostatic composition of the CSF. The CSF fills the ventricles of the brain, the spinal medium and subarachnoid space. In humans, the total volume of CSF is roughly 140 ml which is replaced four to five times daily [30]. Because the endothelium in the blood capillaries in the CP is fenestrated, resistance to drug transport seems to be produced by (gap) - junctions of the CP- epitheliums, which are more passable than the tight junctions of the BBB-endothelium. Also, blood flux in the CP- blood capillaries seem to be 5 to 10 times advanced than the mean cerebral blood flux [24]. In addition, it has been calculated that the total face area of the entire CP is in the same order of magnitude as the entire BBB [31]. The total volume of CSF relative to the brain size is also important advanced in developing brutes than in the grown- up [34]. Adult mortal brain has roughly 100-140 mL of CSF and the rate of CSF product is analogous to the rate of CSF absorption into the supplemental blood aqueduct, which is about 20 mL/ hr. therefore, the entire CSF volume in the mortal brain is cleared every 5 hours [35].

1.4. Blood Tumor Barrier

When there is CNS malice, intracranial medicine administration becomes more difficult. BBB exhibits clinical results in the CNS tumors microvasculature. In CNS cancers, the physiological walls help drug transport through the circulatory system [23]. Intracranial medicine delivery is indeed more difficult when the target is a CNS excrescence. The presence of the BBB in the microvasculature of CNS excrescences has clinical consequences. For illustration, indeed when primary and secondary systemic excrescences respond to chemotherapeutic agents delivered via the cardiovascular system, intracranial metastases frequently continue to grow. In CNS malice where the BBB is significantly compromised, a variety of physiological walls common to all solid excrescences inhibit medicine delivery via the cardiovascular system. Drug delivery to neoplastic cells in a solid excrescence is compromised by a miscellaneous distribution of microvasculature through-out the excrescence interstitial, which leads to spatially inconsistent medicine delivery. Likewise, as an excrescence grows large, the vascular face area decreases, leading to a reduction in trans-vascular exchange of blood-borne motes. At the same time, intra-capillary distance increases, leading to a lesser diffusional demand for medicine delivery to neoplastic cells and due to high interstitial excrescence pressure and the associated peri-tumoral edema leads to increase in hydrostatic pressure in the normal brain parenchyma conterminous to the excrescence. As a result, the cerebral microvasculature in these excrescence conterminous regions of normal brain may be indeed less passable to medicines than normal brain endothelium, leading to exceptionally low redundant-tumoral interstitial medicine attention. Brain excrescences may also disrupt BBB, but these are also original and nonhomogeneous dislocations [28]. It's assumed that the blood-brain-tumor barrier (BBTB) confined the distribution of medicines from blood to brain excrescence [08].

2. CNS disease and nanomedicine for CNS diseases

2.1. Alzheimer's disease

Alzheimer's disease, the most common habitual progressive neurodegenerative disease among the elders especially over 65 times old, is characterized by unrecoverable cognitive dysfunction, behavioral impairment, and madness as complaint advances. It's estimated that roughly 47 million individualities suffer from madness each over the world, among which nearly 36 million have announcement and the number is projected to increase by 131 million till 2050 [36]. Individualities with announcement suffer from progressive memory loss, superintendent function impairment, and language deterioration and ultimately die from announcement due to significant neuronal loss [22]. A therapeutically applicable conception in announcement is grounded on the supposition that brain and supplemental blood announcement are in equilibrium with each other. Hence, the junking of amyloid-β (Aβ) from the fringe is anticipated to affect in an equilibrium shift, with consequent reduction of Aβ in the brain [37]. Neurons in other corridor of the brain are ultimately damaged or destroyed, leading to difficulties in performing introductory functions of the body, similar as walking and swallowing [38].

2.2. Parkinson's disease

Parkinson's disease (PD), the alternate most common neurodegenerative conditions, is characterized by motor abnormality including bradykinesia (slowness of movement), earthquake at rest, severity and postural insecurity [36]. About 90 – 95 of PD cases don't appear to have an inheritable base, whereas 5 – 10 of the cases are linked to inherited mutations and half of early-onset PD is caused by loss of function mutations in the parkin gene, which encodes an E3 ubiquitin ligase. Despite all these attestations, the etiology of the complaint remains unknown [37]. Several mechanisms have been linked to play crucial places in PD complaint progression, and these include α- synuclein misfolding and aggregation, mitochondrial dysfunction, dysfunctional protein concurrence systems, the ubiquitin – proteasome system, and autophagy – lysosome system, and neuroinflammation [39]. Enhancing the position of dopamine in the brain is the most common treatment to ameliorate the symptoms in PD cases; still, this treatment does not alter the progression of the complaint or restore the affected dopaminergic neurons [40]. The onset of PD before the age of 50 is rare and the complaint hits a peak frequence of roughly 4 in old age groups. PD is a complex neurological condition characterized by motor and no-motor poverties similar as bradykinesia, resting temblors, severity, and postural insecurity. In the pathogenesis of PD, there's a picky and progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), that design into the rudimentary ganglia which causes the forenamed symptoms of PD [41].

2.3. Ischemic Stroke

Ischemic stroke is a pathological condition in which there's inadequate blood force due to inhibition of cerebral vasculatures similar as embolization and thrombosis. It's reported that ischemic stroke, with high morbidity, disability, and mortality, is the leading cause of death and disability worldwide. In the United States, it's estimated about 800,000

people suffer from strokes annually in which ischemic stroke accounts for 87%. Current individual styles for ischemic stroke substantially calculate on clinical symptoms as well as CT and MRI examinations of the brain [36]. Accounting for further than 80% of all strokes, acute ischemic stroke is caused by a thrombotic or embolic occlusion of a major cerebral roadway (generally the middle cerebral roadway), or its branches, performing in a flash or endless cerebral blood inflow reduction, and driving a metabolic waterfall of events that, unless instantly reversed, crown in unselective neuronal cell death within the affected towel [37]. This indicates that subarachnoid hemorrhage leads to diseases of the glymphatic system and related pathological damage [42]. The ischemic stroke is delicate to cure because of severe cerebral infarction caused by ischemia and reperfusion [43].

2.4. Tumor

Gliomas refers to a broad category of primary tumor, which are began from glial cells that regard for 30% of all brain tumor and 80% of primary malignant brain tumors [37]. The brain is susceptible to numerous primary and secondary (also known as the metastasis) tumors. It's estimated that the prevalence of cancer in the brain is 3.5 per 100,000 worldwide and there are averagely around new nasty brain excrescence cases in one day. According to the World Health Organization bracket, there are roughly further than 60 types of primary excrescences, among which a glioma, counting for 60 of overall primary brain tumor, is the most common form of aggressive brain malice. In recent times, rapid-fire advances in numerous imaging modalities allow them to be applied to the opinion of gliomas [36]. Cases diagnosed with the most common and aggressive form of these tumors, nominated glioblastoma multiforme (GBM), has a median survival of lesser than 2 years. [01].

2.5. Huntington disease

Huntington's Disease (HD), also known as the Huntington's chorea, is a common autosomal dominant inherited complaint that arises from mutation of the Huntingtin gene. The mutation leads to product of aberrant Huntingtin protein, which is toxic to cells, but the exact medium responsible for HD remains unclear. The incarnation in HD varies among different cases and stages including absence of collaboration, rapid-fire and involuntary body movements, and internal disability similar as progressive cognitive decline and indeed psychosis [36]. Neurons begin to die because of abnormal Huntington’s proteins that are produced abnormally by Huntington’s genes, which are also known as complaint - causing genes [44]. HD is characterized by the aggregation of a mutant protein huntingtin in the neurons, leading to indecorous neuronal function and eventual neuronal death, which led to abnormal movement in cases (i.e. Chorea) [45]. Huntington’s affects an individual substantially in their adult times at around 45 times of age, precipitously surpassing the victim’s motor and cognitive functions as well as impacting the behavioral pattern [46].

2.6. Sclerosis and migraine

Multiple sclerosis is a progressive autoimmune inflammatory disease characterized by demyelination and subsequent death of neurons. Lymphocyte infiltration into the CNS triggers autoimmune and inflammatory responses and selectively destroys oligodendrocytes, which are responsible for myelin production, therefore mediating the demyelination process [47].

A migraine is an intermittent unilateral or bilateral shifting headache. Cortical spreading depression (CSD) is an implicit signal that waveform can be characterized by an intense neuronal activity that slowly progresses over the cortex and a period of neuronal inactivity [42].

2.7. Neuropathic pain

Neuropathic pain is a habitual pain state that generally results from nerve fiber dysfunction or damage, because of central or peripheric nerve injury. This condition is secondary to several conditions, from trauma injury to multiple sclerosis, has a high frequence worldwide, and is extremely delicate to treat. Although not surely characterized in terms of cell mechanisms, incorrect pain signaling results from activation of astrocytes and microglia, which causes neuronal sensitization following supplemental nerve injury [37].

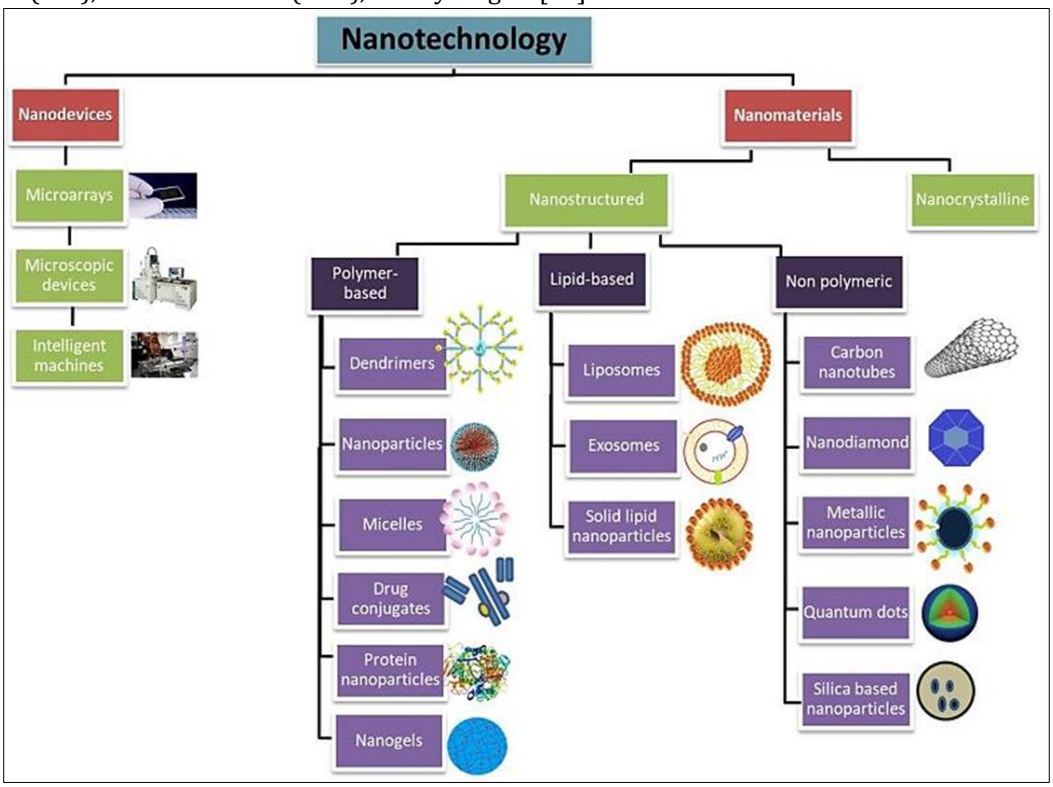
2.8. Ideal properties of Nanoparticles for crossing CNS: [32]

- Biocompatible, Nontoxic, and biodegradable.
- Nanoparticle with small size, ranging from 1 -100 nm.
- Scalable and affordable manufacturing process.
- Amenable to small molecules, peptides, proteins or nucleic acids.
- Physical stability both in vivo and in vitro.
- Avoidance from RES (Reticulo-endothelial system) which prolongs blood circulation time.

- CNS targeted delivery via receptor-intermediated transcytosis across brain capillary endothelial cells.
- Formulation stability, minimal nanoparticle excipient-induced drug modification (chemical declination/ modification, protein denaturation)
- Ability to protect drug from degradation & Controlled-drug release properties.

2.9. Nanoparticle based drug delivery systems for CNS disorders

One of the most significant uses of nanotechnology in medicine is drug delivery (nanomedicine technology). For nanotechnology-based systems, the most common drug delivery techniques observed are oral, injectable, topical, or inhaled formulations. Measuring in nanometers (nm), these polymer-based nanocarriers and nanovectors can deliver multiple drugs [05]. Treatment options are limited substantially due to the incapability of medicines to cross the blood – brain barrier (BBB) or their poor solubilities by oral route. Numerous strategies have been developed to overcome the BBB, similar as medicine delivery systems, liposomes, polymeric and solid lipid NPs (SLNs), solid lipid carriers, liquid chargers (LCs), microemulsions (MEs), and hydrogels [48].



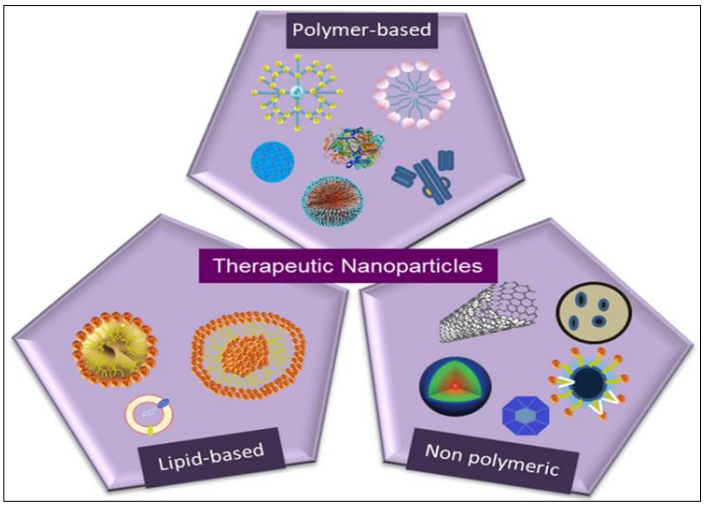


Figure 3 NPs based drug delivery system [05]

3. Lipid based

3.1. Liposomes

Liposomes were developed in the 1960s by Bangham et al. discovery. They are artificial phospholipid vesicles consisting of one or more phospholipid bilayers surrounding an aqueous space, varying in size from 20 to 5,000 nm or even larger and can be loaded with therapeutic agents [05]. Liposomes may contain a single lipid bilayer or multiple bilayers around the inner aqueous cube and are thus classified as unilamellar and multilamellar, respectively. Liposomes are classified by their lamellar size as small unilamellar vesicles with compasses of 20 – 100 nm, large unilamellar vesicles with compasses exceeding 100 nm, giant unilamellar vesicles with compasses up to 1 μm, oligolamellar vesicles with compasses of 0.1 – 1 μm, and multilamellar vesicles with compasses up to 500 nm [48,49]. Different liposome combinations can be integrated to give a targeted Multi-drug delivery platform that's largely material for the drug of any multi-factor disease [50]. They're presumably the most studied and clinically honored nanocarriers owing to their long track record, low toxin, and capability to deliver both hydrophilic and lipophilic composites nicely well [30].

3.2. 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 condition of the cell. Exosomes are primarily involved in intercellular communication and can control inflammation, autoimmune, and T-cell-mediated immune responses. The pathophysiology of neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, and even prions is linked to exosomes. Nonetheless, native exosomes derived from mesenchymal stem cells (MSCs) continue to be able to facilitate immunological regulation, migration, homing, and neurite remodeling. According to recent research, in models of Parkinson's and Alzheimer's diseases, modified MSC-derived exosomes, or MSC-exos, moved to disease regions of brain. [51]. The advantages offered by exosomes as a vehicle for medicine delivery include: (1) Small motes and biologicals can be reprised into the exosomes,(2) exosomes can cross physiological walls, and target towel through their natural face proteins,(3) they give broad distribution in natural fluids, therefore perfecting rotation time and efficacity, and (4) they offer an bettered safety profile and selectivity over polymeric nanoparticles and liposomes[52].

3.3. Solid lipid NPs

Solid lipid nanoparticles are generally constituted by a matrix of lipids that remain solid at room and body temperature [41]. SLNs are generally spherical, with average compasses between 10 and 1,000 nm when dispersed in water. SLNs retain a solid lipid core matrix that can solubilize lipophilic molecules. Lipid core is containing mostly triglycerides (eg, tristearin), diglycerides (eg, glyceryl behenate), monoglycerides (eg, glycerol monostearate), adipose acids (eg, stearic acid), steroids (eg, cholesterol), or waxes (eg, cetyl palmitate) [48]. SLNs developed nearly 15 years ago, SLNs are made up of solid lipids that are dissolved in water and stabilized using emulsifiers. SLNs are made with emulsifiers (polysorbates, poloxamers, and bile salts) and solid lipids that are frequently utilized in the food company. To get around some of the issues that polymeric NPs have with being nanoparticulate drug carriers, SLNs have been recommended as an alternative [05]. Stearyl alcohol, monostearate glycerol, monostearin, and stearic acid are among of the important lipids used in presentations, while Tween, Span, and poloxamer are some of the well-known surfactants that also serve as stabilizers. The proper choice of lipids and surfactants, as well as the composition of SLNs, affect the physicochemical properties of these materials [50].

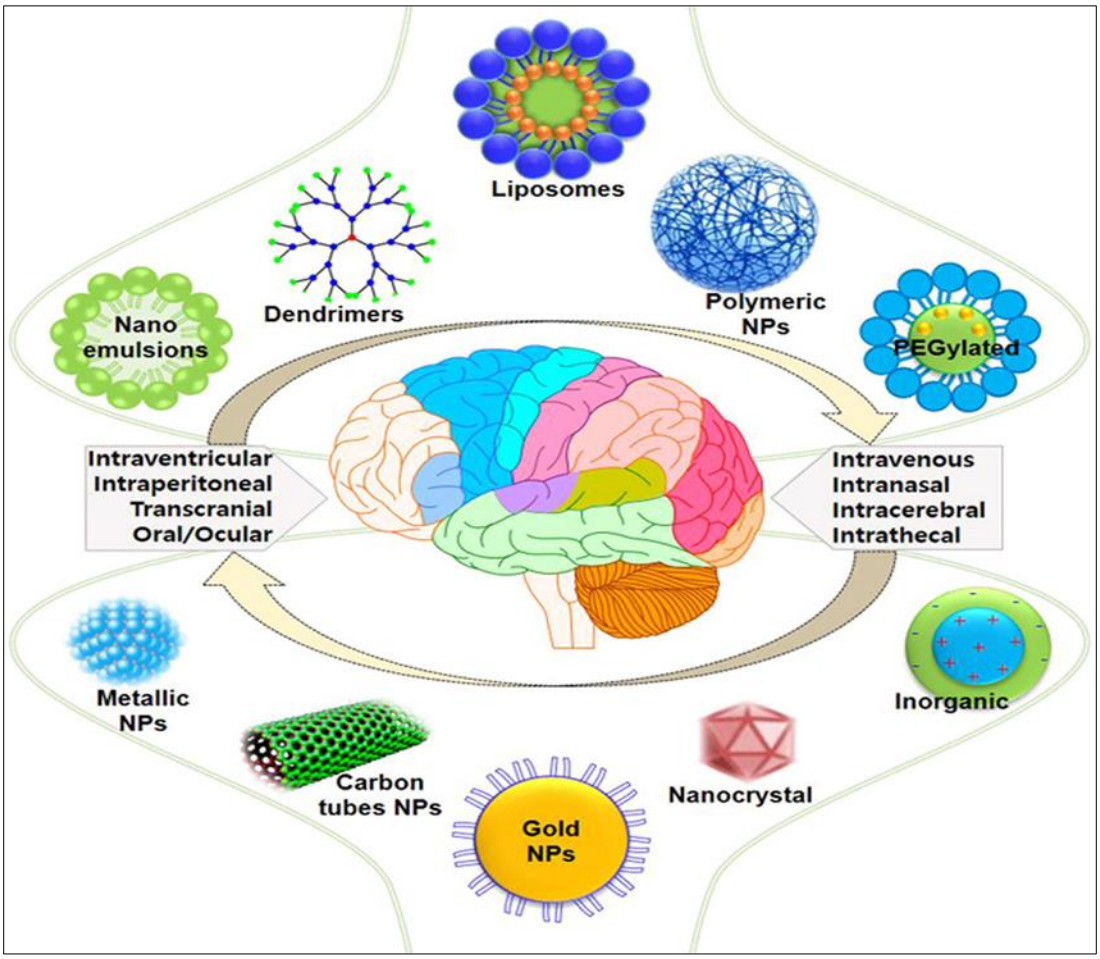


Figure 4 Nanotechnology-based drug delivery system approaches on treatment of CNS disorders [53]

4. Polymer based

4.1. Polymeric NPs

It can be achieved to develop polymeric nanoparticles using a range of materials, such as carbon nanotubes, lipids, polymers, and ceramics. Polymer materials, when compared to other compositions, possess an ideal combination of properties [54]. Polymeric nanoparticles represent the most pioneering approaches for medicine delivery operations, substantially for NDs [46]. It was also shown that anti-tumor antibiotic, doxorubicin, could be delivered into the brain with polysorbate 80-carpeted PBCA nanoparticles after intravenous administration in healthy rats, yielding high whole brain attention of 6 μg/g doxorubicin. In discrepancy, doxorubicin in result form without and with polysorbate 80 or doxorubicin bound to uncoated nanoparticles remained below the discovery limit (0.1μg/g) when used as controls [02]. The nanoparticulate expression of doxorubicin also enabled a considerable excrescence growth reduction in an experimental rat glioblastoma model [35].

4.2. Nanoparticles

The therapeutic drug is either coated on the particle surface by conjugation or adsorption, or it is entrapped within the colloid matrix of nanoparticles (also known as nanospheres), which are colloidal systems with compact structures. For this reason, many nanoparticles can deliver controlled, long-lasting medication release. Most nanoparticles are composed of lipids, polymers, or a combination of the two [30]. Medicines could be defended from elimination by using encapsulation with the semipermeable membrane of synthetic polymer, nanofibers, and three-dimensional polymeric structures [25]. NPs can be made of a broad number of accoutrements , including poly(alkyl cyanoacrylates) (PACAs) similar as poly(butyl cyanoacrylate) (PBCA) and poly(hexyl cyanoacrylate) (PHCA); poly(methylidene malonate); poly(methyl) methacrylate PMMA); acrylic copolymers; polyesters similar as poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and their copolymers similar as poly(lactic-co-glycolic acid)(PLGA); poly(ε- caprolactone); but also

polysaccharides(e.g., dextran, chitosan), proteins(e.g., albumin), etc. Some of these polymers and copolymers similar as PLA, PGA, and PLGA have been approved by the FDA [05].

4.3. Nanogels

Nanotechnology has come up with advancements in hydrogel technology by introducing smart nanogels, which have further advanced properties than bulk three-dimensional cross-linked hydrogels. Nanogels are the nanoparticle form of hydrogels in the range of 1 −100 nm. Every nanocarrier has unique qualities and advantages over other types. For preclinical applications, the nanocarriers that have been covered thus far have drawbacks for preclinical uses; for example, liposomes require strict storage conditions and improved stability. Drug burst release problems are associated with polymer particles of poly(lactic acid-glycolic acid) copolymer (PLGA), and questions remain regarding the toxicity and biodegradability of inorganic nanocarriers. According to studies, nanogels offer high biodegradability, high biocompatibility, high stability, and convenient storage conditions, which significantly overcome these drawbacks. Study indicates that administering nanogels intravenously can improve the brain's absorption of insulin. [51]. Nanogel's modification Insulin and transferrin on the skin's surface improve BBB distribution. Azadi and coworkers created a novel methotrexate formulation based on nanogel technology [25]. The oligonucleotides transported more readily through the cell monolayers after being incorporated into nanogels [55].

4.4. Micelles

Micelles are summations of amphiphilic particles dispersed in a liquid phase. An inadequately water-answerable, lipophilic emulsion can be solubilized in the micelle core region for easy administration. Micelles made of Pluronic block co-polymers are the most studied micellar nanocarriers. Their effect on bettered medicine transport across the BBB was demonstrated in both in vitro and in vivo studies [30]. The amphiphilic particles in micelles are in constant exchange with those in the bulk result. On the other hand, polymeric micelles, also known as polymersomes, are tone-assembled polymer shells composed of block copolymer amphiphiles similar as polyethylene glycol- polylactic acid (cut-PLA) and cut- polycaprolactone (cut- PCL) [56].

4.5. Dendrimers

The tiniest, well-defined nanoformulations, dendrimers, have therapeutic uses in the biomedical field to treat NDs. Numerous nanocarriers for the delivery of drugs or genes to the brain can be produced by modifying any one of the dendrimer's properties, including size, core-shell structure, and surface functional groups. Additionally, dendrimers' substantial antiamyloidogenic action offers a promising alternative for the treatment of prion diseases, Parkinson's disease, and Alzheimer's disease [46]. When treated with nanomedicines, the major challenge for glioblastoma multiforme curatives is poor penetration and posterior retention of nanoparticles in the glioblastoma parenchyma. The size of the nanoparticle can vastly impact the delivery effectiveness in the excrescence towel. Decreasing the nanoparticle size can improve the nanoparticle penetration in excrescence towel but drop the nanoparticle retention effect. Thus, small nanoparticles with a high retention effect in excrescences are urgently demanded for effective glioblastoma multiforme medicine delivery [52]. Dendrimers are modified with spacers or liaison on the face to ameliorate biocompatibility, softening capacity, half- life, and medicine- release kinetics [57]. Dendrimers could be effective medicine delivery vehicles for brain injury and neuroinflammation therapy similar as TBI, ischemic brain stroke and in brain excrescence. Beast models of ischemic grown-up and bambino strokes, ischemic optical neuropathy and brain injury related to cardiac arrest have shown accumulation of dendrimers in injured brain [04].

4.6. Hydrogels

Hydrogels, which consist primarily of water in three-dimensional polymeric networks, have demonstrated remarkable efficacy in offering neuroprotective properties. To achieve focused activity in NDs, hydrogel formulations are either intended for local administration or systemic distribution into the brain. Hydrogels loaded with activin B have been produced recently by Zhang and his colleagues to treat Parkinson's disease. The findings showed a 5-week period of gradual activin B release. The study found that substantial cellular protection led to behavioral improvements. The related review articles cover several of more examples of hydrogel-based drug delivery systems (DDS) for the treatment of neurodegenerative diseases. [46].

5. Current approaches and Challenges

Significant Sweats are presently underway to explore substantiated nanomedicine approaches to treat or manage CNS conditions. Still, numerous of the developments are still in the original stages and bear more-detailed preclinical testing in a range of beast models. Safety, efficacity, and nonsupervisory issues are major challenges for the progression of substantiated nanomedicine to treat CNS conditions in the clinic. The styles used to deliver medicines to the brain have

been optimized by opening the BBB non-invasively on applying external stimulation (e.g., ultrasound, electromagnetic fields), but are known to affect in colorful neurobehavioral or other affiliated adverse goods [58]. Generally, utmost rectifiers of CNS conditions in conventional administration enter the CNS via the systemic blood rotation. To reach effective medicine attention at the CNS complaint spots, it's necessary to raise the systemic medicine situations by mainly enhanced cure or extended administration [13]. Major challenges include effectively bypassing the BBB, perfecting towel, and cell-specific targeting, and enhancing cellular uptake and endosomal escape [17]. The creation of protein-nimbus is known to be a barrier to the advancement of individual and remedial nanoparticles for in vivo operations. Serum proteins that gather around nanoparticles can hinder their targeting effectiveness [59]. Recent in vitro studies have shown that not only the NP face charge has an influence on the paralyzed protein nimbus but also the size. The influence of different flyspeck parcels on protein list was anatomized in detail by several exploration groups [60]. Therefore, in the near future, an evaluation of the safety and efficacity of suitable NPs through mortal clinical trials can lead to promising, cost-effective announcement rectifiers [61]. Nanotechnology may also have a part in perfecting delivery of boron to brain excrescences and in enhancing the effectiveness of neutron prisoner remedy. Boron neutron capture therapy (BNCT) involves the inauguration of nuclear responses in the presence of boron-10 and free low-energy thermal neutrons. Boron-10 captures these neutrons to yield high linear energy transfer (LET) nascence patches and flinching lithium- 7 capitals, which, in turn, kill excrescence cells. Neutron prisoner remedy presently depends on the use of the low molecular weight agents, sodium borocaptate and boronophenylalanine. Studies exposing cells to boron containing nanocarriers have shown promising goods, including more specific targeting of excrescence cells, reduced toxin to healthy cells, and significant saturation through the BBB [62].

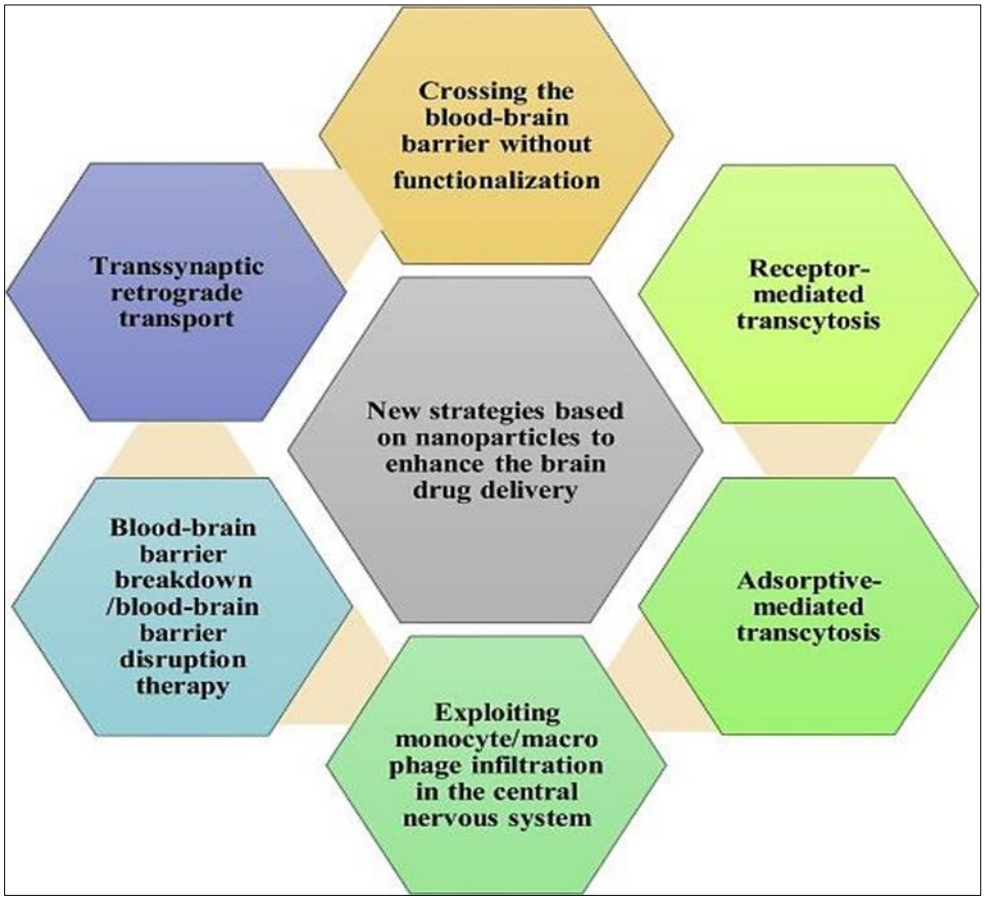


Figure 5 Developments of new strategies based on NPs technology for drug delivery to the brain [25]

6. Future prospective and strategies

Nanotechnology provides a unique justification to combat cancer on the molecular scale through careful engineering of nanomedicines to specifically interact with cancer cells and inhibit cancer cell function. Still, a nanoparticle system could be effective against CNS disease if it could pass through the blood- brain barriers, find the CNS lesion, target excrescence cells specifically, and release a cargo of remedial agent without altering the vital functions of the CNS. To deliver particles across the BBB, many invasive and noninvasive styles have been developed and studied, but their clinical effectiveness

has not exceeded that of current treatment styles [62]. CNS diseases represent a broad diapason of brain affections with short and long- term disabilities, leading contributors to the global disease burden. In malignancy of great stride in the advancement of medical technologies and healthcare installations there has been a constant clinical failure to find the endless cure for utmost of the CNS conditions [63]. Targeted gene revision via gene-editing tools (ZFNs, TALENs, and CRISPR/ Cas9) has been arising as a new remedial option for the treatment of neurodegenerative conditions [64]. Advances in nanotechnology have led to a rise in implicit remedial strategies against Alzheimer's disease progression. For Alzheimer's disease nanotherapeutics, a biocompatible nano-carrier with acceptable size, shape, charge, and face characteristics corresponding to the intended point medium of action is needed [65]. The development of drug delivery routes is presently exercising the pathway of the trigeminal nerve [66]. The synthetic DDSs, similar as NPs, liposomes, dendrimers, micelles, nano capsules, nano sponges, peptide- grounded nanoparticles etc. have good medicine encapsulation effectiveness (EE), drug loading (DL) capacity, inflexibility in functionalization, easy/ robust product, and theragnostic functions. Still, conjugation of a cut polymer, peptide, antibody etc. may develop medicine forbearance [67]. The high failure rate of medicines to treat CNS conditions has led to business opinions by some large pharmaceutical companies to discontinue drug development in this space [68]. Despite these implicit advantages, nanocarrier-intermediated drug delivery has some demanding aspects, including safety, product, and regulations [39]. Medicine delivery to the brain can be achieved via several styles, including original invasive (direct injection/ infusion) delivery induction of enhanced permeability and the operation of global physiological targeting strategies [31]. The therapeutic potential of nanomedicine will calculate on the rational approach and farther designing of nanomaterials grounded on detailed and comprehensive knowledge of attained from natural processes [69]. Thus, studies are in progress to manufacture NPs, exosomes, and ligands in an applicable rate, and contingencies similar as cut covert technology have evolved, making hybrid nanomedicine, a combination of NPs and EVs, an effective direct delivery system [70]. CSF endothelin-1 situations are elevated in HIV- 1, ischemic stroke, and subarachnoid haemorrhage, and relate with the inflexibility of HIV encephalopathy. Therefore N- acetylcysteine or other controllers of endothelin- 1 release have the implicit to affect a range of complaint conditions while acting on the luminal face of the BBB [20].

7. Conclusions

Liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles are many examples of the several types of nanoparticles that have been created and may be altered to amend targeting to certain brain regions, increase stability, and optimize medicine release patterns. Openings in nanoparticle medicine delivery for CNS diseases include using the enhanced saturation and retention effect, employing active targeting strategies, achieving responsive medicine release, developing multimodal imaging and therapeutic agents, and utilizing personalizing drug approaches. In recent decades, scientist have been suitable to design nano formulations of plain or crosslinked polymer, lipid, or inorganic accoutrements with hydrophilic, hydrophobic, or amphiphilic nature, variable surface properties, loading hydrophilic or hydrophobic medicine contents and decorated with multifunctional ligands to attack the natural walls, and ameliorate the safety and efficacity of brain therapeutics.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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