2023 • Vol. 1, No. 1 • pp. 34-47
Trends in Pharmaceutical Biotechnology (TPB)
ISSSN: XXXX-XXXX

Nanocarriers and Beyond: Innovations in Overcoming Barriers for Effective CNS Drug Delivery

Shahad Q. Al-Hamadiny[1,*], **Rasha Ibrahim Salman**[1], and **Ali Mohammed Al-Rawe**[2]

[1]*Department of Biotechnology, College of Science, University of Wasit, Wasit, 52001, Iraq.*
[2]*Department of Biotechnology, College of Science, University of Anbar, Ramadi, 31001, Iraq.*
[*]*Corresponding author name: Shahad Q. Al-Hamadiny, Email:*sahadqasim91@gmail.com

Access this article online

REVIEW ARTICLE
Received: 01.05.2023 **Revised:** 30.05.2023
Accepted: 09.06.2023 **DOI:** 10.57238/tpb.2023.144275.1003

OPEN ACCESS

ABSTRACT

Although numerous medications have the potential to treat central nervous system (CNS) disorders, only a small number of these drugs have actually been used successfully. It is as a result of the blood–brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSF) preventing them from exerting biological activity by allowing them to cross the brain. The current methods for enhancing penetration across these barriers for efficient CNS medication delivery are reviewed in this article. Direct systemic delivery, invasive delivery, BBB disruption, and convection enhanced delivery are a summary of these problems. Additionally, cutting-edge nanoscale drug delivery methods such polymeric nanoparticles, liposomes, nanoemulsions, dendrimers, and micelles are explored. These nanocarriers might lead to a development in the treatment of numerous CNS illnesses. To evaluate the biocompatibility and safety of these medical devices, however, further extensive research is required.

Keywords: Nanotechnology, Drug delivery system, Central nervous system

1 INTRODUCTION

In the past twenty years, there has been a noticeable and substantial advancement in the diagnosis and treatment of CNS diseases. Nonetheless, conditions affecting the CNS like AD, PD, neuroinflammation, neuro-AIDS, and MS, remain the primary cause of disabilities, work incapacity, and premature mortality worldwide. The main challenge in addressing these conditions lies in the fact that numerous medically approved medications have lost their effectiveness due to their incapability to efficiently penetrate the brain and reach the brain tissue for delivery. The BBB is an exceptional and complex endothelial barrier that guards the brain from potentially hazardous chemicals. The BBB is composed of meticulously arranged monolayers of polarized ECs that exhibit glycosaminoglycans attached to proteins and lipids within the cell membrane, along with membrane receptors and enzymes. The endothelial lining of the capillary wall contains specialized transporters that facilitate the transfer of primarily amino acids, glucose, and FFA to adjacent neurons [1]. Capillary endothelial cells are enveloped by a dense network of strong interconnections, with complex TJs being the most well-known among them. The structural integrity of the brain barrier enables it to carry out several important roles, including providing vital nutrients like glucose and amino acids, protecting against the effects of neuroactive chemicals and poisons, and allowing the interchange of chemical substances between the CNS and the circulatory system. In recent years, significant endeavors have been undertaken to comprehend the mechanisms of drug transportation and delivery to the CNS. Several studies were carried out to explore the operation of the intact and impaired BBB, leading to the identification of key factors influencing this process [2]. Precise understanding of drug transportation to the brain plays a pivotal role in developing drugs for CNS disorders. Various disease and pathological conditions have a significant impact on the drug delivery process since the possession of the BBB undergo changes during neurological disorders, inflamma-

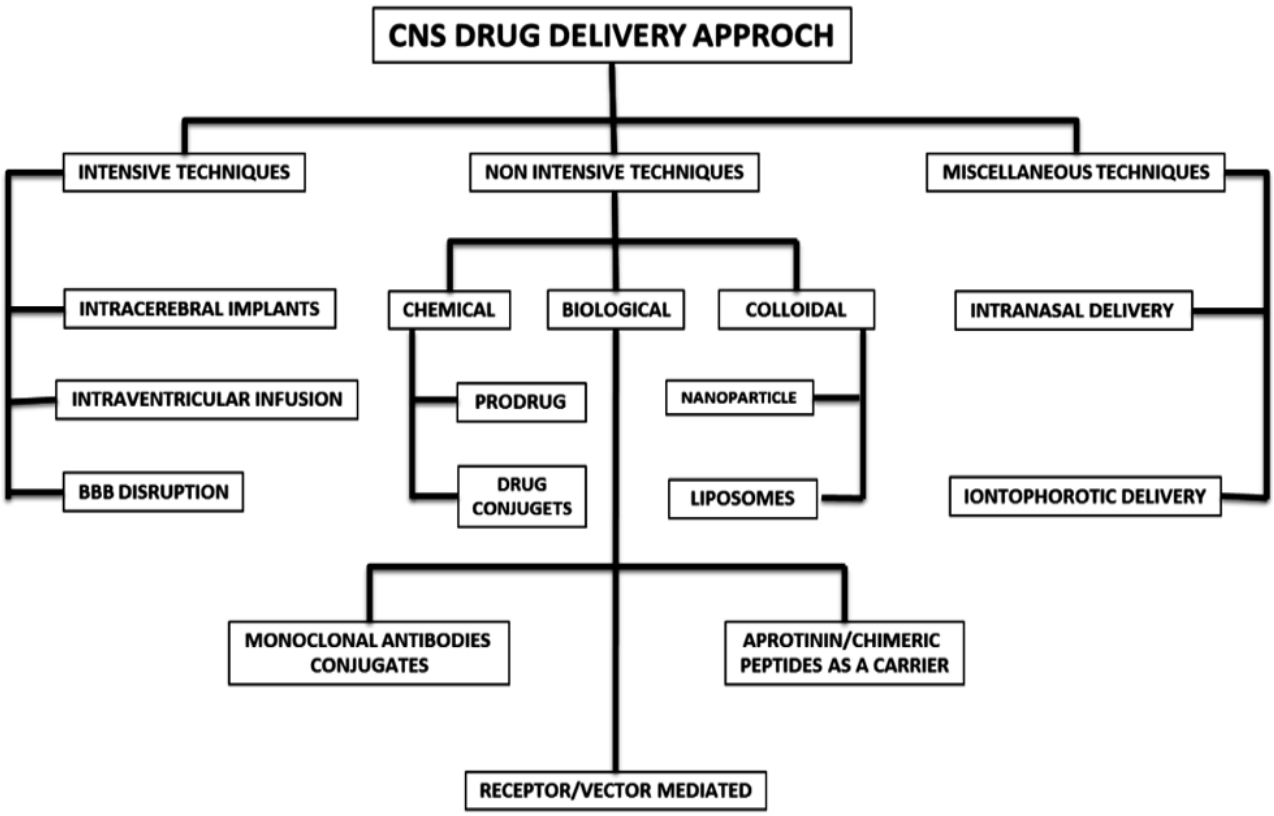

Fig. 1. CNS drug delivery approach.

tory situations, or infections caused by bacteria, fungi, or viruses. These changes influence the integrity and function of the BBB, includes receptor and transporter expression and performance. Studies have indicated that the drug delivery process is modified under pathological conditions, possibly due to alterations in various transport pathways like transcellular transport and paracellular transport [3]. Indeed, a compromised BBB can create a favorable chance for drugs that typically cannot penetrate the BBB to access specific targets within the brain tissue.

At present, there exist multiple strategies available for brain drug delivery, encompassing invasive, pharmacological or biological, chemical, and physiological approaches (Fig.1). Invasive techniques involve the introduction of intraventricular medications, intracerebral implants, or manipulation of the BBB. The alteration of pharmacologically active substances through chemical modification has commonly been employed to improve the physicochemical properties of drug compounds. The development of highly permeable substances is a result of improving specific physicochemical properties such ionization, molecular size, lipophilicity, polar surface area, hydrogen bonding, and affinity for plasma proteins [4]. Another strategy that has been used to enhance the CNS transport of low molecular weight medicines is the prodrug approach. However, this particular approach is not covered in detail within this study [5,6]. Conversely, to enable targeted drug delivery to the brain, the biological approach involves coupling a drug with antibodies. The antigen located on the BBB is the target of these conjugates. Molecular Trojan horses, chimeric peptides, and vector-mediated transport are other biological approaches. The physiological strategy for brain drug delivery uses built-in transport systems that traverse the BBB. This strategy involves differentiating RMT, CMT and AME. This review focuses on recent methods explored for efficiently transporting therapeutic and diagnostic factors to the brain. The main stress lies on two approaches: direct systemic delivery and invasive delivery, encompassing techniques like Convection-enhanced delivery and BBB disruption. The article also analyzes and discusses cutting-edge nanoscale medication delivery methods [6].

2 Direct systemic delivery

Drug delivery directly to the CNS via systemic routes can be classified into two types: invasive and non-invasive methods (Fig.2, Table 1).

Present-day studies in CNS drug development primarily focus on two main areas: the enhancement of systemic drug delivery to the brain and the strategies to overcome or disrupt the BBB. Nanotechnological systems or devices can also facilitate systemic delivery. It is noteworthy that

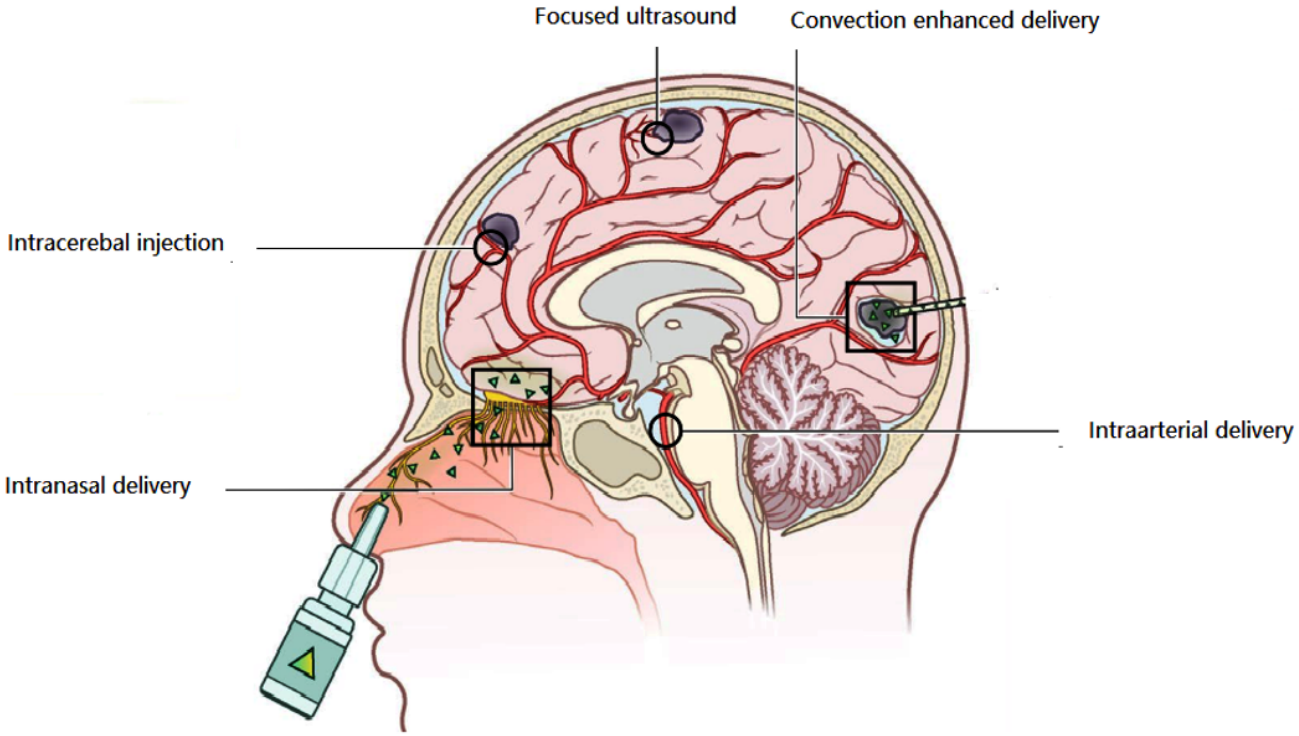

Fig. 2. A summary of the current drug delivery techniques for the treatment of primary brain tumors.

drugs with low likelihood of crossing the BBB can be encapsulated in liposomes or other drug delivery systems to enhance their lipophilicity [13].

2.1 *Intranasal delivery*

Medicines managed intranasally utilize the olfactory-sensory neurons as a route of transportation. Through this pathway, they can reach considerable concentrations in the CSF and the olfactory bulb without being hindered by the BBB. The ability of materials to penetrate is facilitated by the abundant vascularization of the mucosa, propria plaques, and permeable epithelium [14]. The use of intranasal drug delivery enables the transportation of large molecular weight drugs, such as stem cells and proteins, to access the brain. This approach opens up possibilities for treating various diseases, including AD, PD, epilepsy, and critical brain tumors [15]. The drugs are transported to the brain through different methods, encompassing transcellular, paracellular, and neuronal transport pathways [13].

The transnasal method of drug administration offers numerous benefits. By bypassing the first-pass metabolism in the liver, the drug experiences higher bioavailability and reaches the brain more rapidly. Additionally, this approach is simple, non-invasive, and easy for drug administration [14]. In a rat model, researchers demonstrated that intranasal pathway can successfully transfer VIP. A minimum concentration of intact VIP was found in the olfactory bulbs and midbrain just 30 minutes after intranasal delivery, whereas no intact VIP was found in the brain following intravenous injection. This suggests that intranasal administration could serve as an alternative method for delivering neuropeptides that cannot pass through the BBB or are rapidly metabolized in the blood [16]. Furthermore, a study assessing the transfer of siRNA to the brain has confirmed the effectiveness of utilizing nano-micelles derived from polyethylene PEG-PCL copolymers coupled with CPP, MPEG-PCL-Tat.

This effectiveness is particularly notable when employing the intranasal route as opposed to the intravenous approach. MPEG-PCL-Tat significantly decreases the transit time via the olfactory and trigeminal nerve pathways due to its strong nasal mucosal permeability [17]. Currently, there have been numerous animal researches investigating the intranasal administration of antipsychotic drugs. However, there is a lack of sufficient human analyses on this matter. Antipsychotic drugs are distinguished by their limited solubility, which restricts the practicality of intranasal administration to highly potent drugs due to the constrained volume of drug dose that can be administered. Another issue is the potential genetic and morphological toxicity of nanoparticles used as carriers for these kinds of medications, such as polymeric nanoparticles or nanoemulsions [18].

Table 1. Methods and strategies for administering drugs to the central nervous system.

Methods for systemic medication administration to the central nervous system	Methods	Strategy	Ref.
Non-invasive techniques	Chemical	Prodrugs Molecular packaging Chemical drug delivery system Lipophilic analogs	[7]
	Biological	Viral vectors Cell-penetrating peptide-mediated drug delivery Receptor -mediated delivery of chimeric peptides	[8]
	Colloidal drug carriers	SLNs Liposomes Dendrimers Microemulsions and micelles Nanocapsules and nanospheres Polyethyleneimine derivatives Carbon nanotubes, single- multi-walled carbon nanotubes	[9]
	Pharmacological	Intracerebral implants Intrathecal/ Intraventricular / interstitial delivery Biological tissue delivery Ultrasound-mediated blood-brain barrier disruption strategy	[10]
Invasive techniques	Blood-brain barrier disruption	Convection-enhanced delivery Biochemical blood-brain barrier disruption strategy Osmotic blood-brain barrier disruption strategy	[11]
	Alternative routes for central nervous system drug delivery	Iontophoretic delivery Trigeminal and olfactory pathways to the central nervous system, intranasal delivery	[12]

2.2 *Intraarterial drug delivery*

The IA method, in contrast to intravenous or oral drug delivery techniques, offers numerous advantages, primarily by increasing the concentration of the drug within the tumor and speeding up systemic clearance [19]. Among the various strategies developed for delivering drugs through the BBB, this method of drug administration is one of the most commonly utilized. It facilitates the distribution of therapeutic agents through the capillary network surrounding and within the tumor, thereby restricting their transport to an exact region. Hence, this approach lowers the risk of systemic toxicity and shows great promise for treating brain tumors effectively [20]. Furthermore, the IA method of drug administration enables higher drug concentrations and enhanced usefulness at the intended location, though it is suitable only for drugs that can rapidly cross the BBB [21].

An instance of IA drug delivery can be observed in the transportation of stem cells to the brain during crucial AIS. Unlike intravenous and intracerebroventricular delivery methods, this approach is minimally invasive and enables preferential distribution of drugs within the infarct part, as it prevents the stem cells from getting trapped in the lungs or liver. Regrettably, the use of IA route for stem cell administration comes with certain limitations, primarily associated with their size and the potential to worsen cerebral blood flow. Up to now, the investigates have demonstrated the effectiveness of administering MSC through the IA route in treating acute AIS 24 hours after its occurrence. Nevertheless, additional research has revealed that the optimal timing and dosage of stem cells for effective treatment via the IA route are yet to be fully determined. This suggests that further trials are required to achieve successful treatment using this approach [22].

Lu et al. research [23] illustrates that administering RES encapsulated in RES NPs through the IA route is an effective approach to protect against cerebral ischemia/reperfusion injuries. The RES-NPs were observed to avoid brain edema, shield neurons from apoptosis, and promote neurogenesis, which are often linked to a rapid recovery of blood stream following a LAO stroke.

2.3 *Intracerebral injection*

An additional invasive method for drug delivery to the brain is intracerebral injection. This approach hinges on precisely selecting the site of drug injection, allowing the drug to diffuse into the surrounding areas [24]. The use of a tiny amount of the drug administered, less danger of drug leaking outside of the target tissue, and a lower probability of inducing an immune response are what set direct injection apart [25]. The procedure of direct drug administration initiates with the patient's head being anesthetized and immobilized in a stereotaxic frame. The next step involves drilling a hole in the skull and inserting a flexible fused silica catheter or a needle into the brain parenchyma. In order to pinpoint the injection site, stereotactic coordinates taken from the brain atlas and supported by MRI guiding devices are used [26]. Potential uses for direct intracerebral injection include brain tumor gene therapy. To demonstrate, for instance, the efficacy, safety, and ability of a tiny non-enveloped AAV to infect both proliferating and quiescent cells, notably neurons,

investigations using this AAV have been carried out in animals. Preclinical research has explored gene therapy utilizing rAAV for diseases affecting specific brain regions like PD and extensive brain areas such as LSDs. While the study outcomes showed promise, further investigations involving larger patient cohorts are necessary [25]. Stereotaxic injection is an alternative approach for treating drug-resistant epilepsy. In this method, the epileptogenic foci are directly injected with AAV vectors that release galanin and neuropeptide Y. Studies in rodents have demonstrated a considerable decline in epileptic seizures as a result of this treatment [27]. While direct administration of AAV to the CNS induces a milder immune response in patients, neuroinflammatory reactions remain a notable concern. So far, instances of inflammations in the DRG and spinal cord pathology have been stated. The precise cause and procedure behind the neuroinflammatory answer have not been fully understood at this point. In order to reduce the danger of such an inflammatory reaction, a treatment tactic needs to be devised. This strategy should involve either priming the immune system for AAV revelation or minimizing the likelihood of transgene expression in tissues other than the intended target tissue [28].

2.4 *Ultrasound technique*

Transcranial FUS involves briefly permeating the BBB to enable drugs to access specific brain targets. This approach offers the benefit of utilizing a reduced drug dosage to attain an effective concentration within the brain. It is critical to remember that any substance that is circulating in the bloodstream could result in a negative drug reaction. Furthermore, the timing of drug administration relies on the opening of the blood-brain barrier by the transcranial FUS [29]. FUS is a complementary treatment to surgery and radiotherapy. The exact process behind the opening of the BBB through FUS has not been fully understood [30]. However, there are two primary possible mechanisms by which FUS can open the BBB. The initial mechanism involves the power of radiation caused by sonication or microbubble vibration, leading to vasoconstriction, which results in provisional ischemia, thereby weakening the BBB. The second method relies on active vacuolar transport [31]. PET and MRI are the prevailing techniques utilized to check the outcomes of the ultrasound procedure. MRI allows for the visualization of the overall impact of ultrasounds. On the other hand, PET not only monitors tissue activity but also serves as a highly sensitive method to quantify the number of radiopharmaceutical present in a particular tissue [30]. Significantly, it has been observed that the BBB can retrieve within a few hours after exposure to ultrasound [31].

Although FUS has been demonstrated to be secure for improving BBB permeability in a reversible manner, further study is essential to establish the clinical significance of drug delivery using this method. Researchers have investigated the impact of microbubbles and ultrasound on tumor delivery, biodistribution, and therapeutic usefulness of a liposome coated with cleavable PEG that is sensitive to enzymes from the metalloproteinase family. To improve cellular absorption and hasten drug release, the coat was cleaved. The research illustrated that the combination of ultrasound and microbubbles led to greater drug accumulation within the tumor, as well enhanced extravasation and liposome penetration into the extracellular matrix. Interestingly, It was discovered that the ultrasound's strength had no bearing on how deeply the penetration occurred [32]. Brain tumors have been successfully targeted in animal trials using doxorubicin coupled with multifunctional microbubbles made of superparamagnetic iron oxide nanoparticles [33].

The FUS method has been employed to deliver trastuzumab, a monoclonal antibody utilized in the treatment of breast cancer metastases, to the brain. According to studies done on mouse brains, the animals' survival time was significantly increased when trastuzumab was transported by FUS. FUS has demonstrated successful transport of neural stem cells, and current clinical trials are in progress to evaluate its efficiency in delivering amyloid antibodies to patients with AD [34].

2.5 *Convection enhanced delivery*

The CED procedure involves inserting specialized catheters right into the brain tissue. Through pressure-controlled infusion and the aid of stereotaxis, the drug is delivered to the targeted area [35]. The infusion continues for several hours before removing the catheter [36]. Consequently, the drug can penetrate the BBB, allowing for the administration of large macromolecular drugs. The conventional approach also carries the risk of toxicity because it necessitates high systemic doses of medication to get an adequate drug concentration in the brain. In GBM patients, the CED technique has made it easier to directly administer the anti-cancer medication carboplatin into the tumor site. Glioblastoma multiforme cells are more vulnerable to the effects of carboplatin than brain cells, according to in vivo tests, which show that carboplatin has non-toxic effects on brain cells. To establish a proficient infusion technique, several aspects need to be taken into account, including the positioning of the catheter tip, the trajectory of the catheter, the catheter's construction, the volume of infusion, and the flow rate of infusion. Precise definition of these aspects is essential to ensure a safe and effective treatment [37].

Moreover, the CED approach has been effectively utilized to deliver liposomal chemotherapeutics to the CNS in tiny creatures. Tests conducted on mice have indicated that CED enables precise dispersion of liposomal poisons throughout the CNS, bypassing the BBB. To sum up, the outcomes of these medical tests have displayed that employing the CED technique for drug delivery sub-

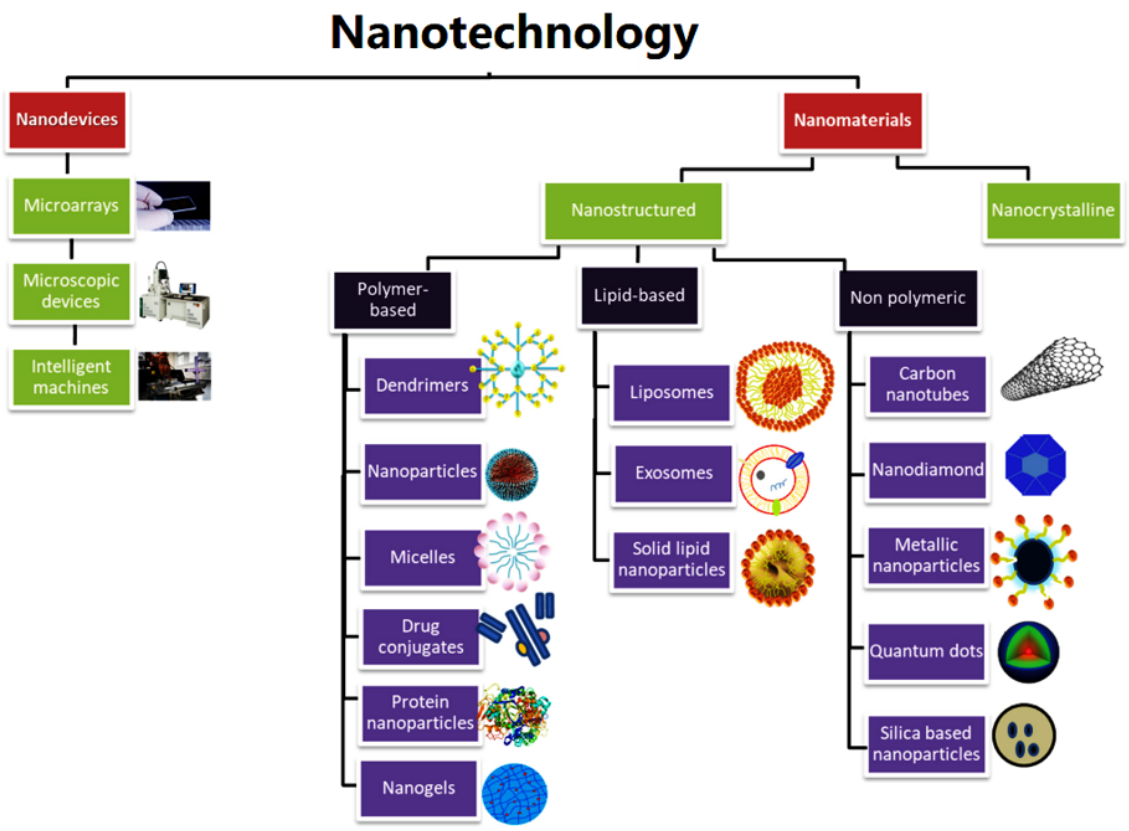

Fig. 3. Components used in medicinal applications of nanotechnology.

stantially enhances drug concentration at the intended location while concurrently diminishing toxicity [38].

3 NANOTECHNOLOGICAL DRUG DELIVERY SYSTEMS

Over the past two decades, there has been considerable enthusiasm for the advancement of biodegradable nanodevices as efficient means of drug delivery. In general, nanostructures aim to deliver a diverse array of drugs to different tissues. These nanodevices can shield the drugs enclosed or linked to them from hydrolytic and enzymatic degradation. In the present era, nanotechnology offers a significant potential for addressing CNS diseases, particularly neurodegenerative disorders. By leveraging nanoscale structures and materials with distinct chemical and physical properties, they can be tailored to execute specific functions, such as breaching the blood-brain barrier or interfering with signaling pathways [39].

The process of crossing the blood-brain barrier is primarily affected by the physico-chemical attributes of NPs, such as their size, shape, stiffness, and surface properties (e.g., surface charge, density of ligands, and targeting ligands) [40]. NPs can be transported to brain tissue through the following mechanisms:

1. NPs can disrupt TJs between endothelial cells or cause localized toxic effects, leading to a localized permeabilization of the BBB and subsequent drug penetration [40];
2. NPs are conveyed across endothelial cells via transcytosis [40].
3. NPs employ endocytosis, releasing their contents into the endothelial cell cytoplasm and subsequently exocytosing on the endothelium abluminal side [41].

Studies have indicated that NPs may employ a combination of the previously mentioned mechanisms. The transcytosis of NPs is facilitated by various receptors, including TfR and LDL receptors [42, 43]. Additionally, cellular transporters such as GLUT1 and LAT1 also play a role in the transport of NPs. The receptors and transporters can be targeted by employing different types of peptides, proteins, or antibodies, which are either physically or chemically attached to the surface of the NPs [6,44]. The ability to alter the surface of NPs is especially crucial due to the fact that numerous neurological disorders e.g., AD and cancer are linked to changes in the expression and function of GLUT1 transporters. As a result, investigations into GLUT1 transporters have been conducted to improve BBB transport, tumor penetration, brain accumulation, and pharmacological effectiveness [40]. As an example, researchers prepared poly (ethylene glycol)-co-poly (trimethylene carbonate) NPs that were functional-

ized with 2-deoxy-D-glucose to investigate the expression profile of glucose transporters in both the BBB and glioma cells. The findings indicated that the developed NPs could be considered as a promising dual-targeted vehicle for brain glioma therapy [45]. In the following section, the primary focus is on carrier systems and the role of some of them in targeted drug delivery to the brain will be examined (Fig.3).

3.1 Liposomes

Drug carriers like liposomes and nanoparticles serve the purpose of enhancing drug effectiveness and minimizing its toxicity. Due to their small size and ability to cross the BBB, these carriers can effectively deliver substantial substances like genes, peptides, or oligonucleotides [46]. Liposomes are minute nanoparticles made up of phospholipids, forming vesicles with one or more concentric layers around a central aqueous core. They adopt a core-shell arrangement, comprising amphiphilic compounds featuring a hydrophilic head group and twin hydrophobic tails. Because of this configuration, liposomes bear likeness to cell membrane structure and are effectively utilized as a modern approach for delivering substances with both hydrophobic and hydrophilic characteristics, including peptides, proteins, and drugs. Lipid bilayers of liposomes are often where lipophilic medications are contained, while aqueous cores of liposomes or the exterior water phase are where hydrophilic pharmaceuticals might be placed.

Based on their size and the number of lipid layers they contain, liposomes can be divided into three groups: multilamellar vesicles with a diameter greater than 200 nm, large unilamellar vesicles with a diameter between 100 and 1000 nm, and small unilamellar vesicles with a diameter below 100 nm [46].

Liposomes are highly valuable when creating therapeutics targeted for the brain due to their biocompatibility, lack of toxicity, and inability to trigger an immune response. The BBB is just one biological membrane that liposomes make it easier to transport medications through, but they also protect the drugs being delivered from being degraded by plasma enzymes. The unique characteristics of liposomes enable customization of their surface through the attachment of specific groups that facilitate drug delivery to the CNS. Surface treatment of nanoparticles with PEG led to this result, which extended their circulation time in the bloodstream. To avoid clumping in solution and to reduce reticuloendothelial system uptake, PEG is added to the surface of liposomes. Additionally, the surface of liposomes can be covered with silk fibroin, chitosan, and PVA [47,48]. The process of opsonization in the plasma and subsequent phagocytic clearance is decreased by using PEG as a protective layer on the surface of liposomes. Advanced stages of ovarian and breast cancer, as well as AIDS, have all been successfully treated with this alteration [38]. Liposomes modified with PEG and carrying sertraline, a medication for depression, were employed to study the speed of its release and its transportation through the BBB using a mouse brain model. Liposome surfaces can also be altered using polysaccharides, ligands, or peptides. This adjustment enables them to effectively traverse the BBTB and selectively target cancer cells. This adaptation has demonstrated success in experiments involving mice with glioma. Treatment with proteolytically stable peptides, specifically (D)CDX (a D-peptide ligand that targets nicotine acetylcholine receptors on the BBB), proved to be more effective than using unmodified liposomes [49]. By attaching to the surface of transferrin, liposomes can assist in transporting 5-fluorouracil, an anticancer drug [46]. Additionally, liposomes are being investigated for their potential in targeted delivery of therapeutics for treating neurological conditions like PD or AD. As an example, liposomes with maltodextrin-coated surfaces were employed as a highly effective carrier for levodopa, a drug commonly used in PD treatment [38].

Over three decades ago, the initial experiments utilizing liposomes for drug delivery in PD were conducted. In these studies, rats with unilateral substantia nigra lesions had liposomes transplanted stereotactically into the striatum as dopamine transporters [33]. According to the study, dopamine-containing liposomes can improve the impairments seen in a mouse model of PD. Furthermore, these findings demonstrated the potential of liposomes as a promising approach for precisely delivering therapeutic agents to specific regions of the brain.

3.2 Exosomes

EVs are tiny, membrane-bound structures involved in intercellular communication and serve as carriers for proteins, lipids, or nucleic acids. These EVs can be classified into three groups based on their size, content, and release mechanism: exosomes, which have a diameter of 40–100 nm; microbubbles, with a diameter of 100–1000 nm; and apoptotic bodies, with a diameter greater than 1000 nm. EVs and Exosomes are released constantly, but their release growths during times of tension, whereas apoptotic bodies are only released due to cell damage. Among these EV types, exosomes have garnered significant interest recently. Exosomes are circular lipid vesicles and constitute a vital component of the cell membrane. Exosomes offer substantial advantages as drug carriers, including their ability to readily traverse the BBB, efficiently penetrate biological barriers due to their small size, widespread distribution in body fluids, and superior safety profile when compared to polymeric nanoparticles [49]. Crucially, the inherent biological nature of exosomes guarantees their excellent biocompatibility, stability, minimal immunogenicity, and low intrinsic toxicity. Exosomes are derived from the inward budding of MVBs, leading to the formation of ILVs. They are then released into the extracellular space through

the fusion of MVBs with the plasma membrane [50].

As previously stated, exosomes can serve as carriers for therapeutic nucleic acids. According to Zhang and colleagues' study [50], exosomes have been found to contain 2838 miRNA,3408 mRNAs, and 9769 proteins. For instance, a study involving the mouse brain made use of exosomes' capacity to carry physiologically active substances. The study investigated the effectiveness of exosomes loaded with hydrophobically modified siRNA administered through ICV infusion for seven days, leading to a significant reduction of up to 35% in Huntington's mRNA levels [51]. In a different study, EVs were employed to transport molecules with poor stability and bioavailability. A notable example is curcumin, renowned for its anti-cancer and anti-diabetic properties [52]. Mice were intranasally managed with exosomes containing curcumin, and over time, a notable decrease in brain inflammation was observed due to the efficient delivery of curcumin to the CNS. Additional experiments demonstrated that curcumin-loaded exosomes also provided protection against LPS-induced brain inflammation [53]. In a broader sense, adapted exosomes are especially appropriate for achieving targeted drug delivery to specific tissues and cells, enhancing drug concentrations in the brain, and improving the efficacy of treatments for neurodegenerative disorders and CNS tumors [50]. As an illustration, Qu et al. [54] effectively transported dopamine to the striatum and substantia nigra using exosomes derived from the bloodstream. On the other hand, using macrophage-derived exosomes carrying glial cell-line derived neurotrophic factor, Zhao et al. [55] observed a reduction in neurodegeneration and neuroinflammation in animals with PD.

3.3 Polymeric nanoparticles

NPs are solid colloidal dispersions consisting of PACA, PLGA, and PLA, which are biodegradable and biocompatible polyesters. These types of NPs are the most commonly employed for drug delivery purposes. Polymeric nanoparticles typically range in size from 10 to 100 nm [81]. These nanoparticles are composed of a dense polymer matrix core that accommodates lipophilic drugs, along with a hydrophilic corona that ensures steric constancy [38]. Drug molecules may be chemically bound, encapsulated, or adsorb to the surface of NPs. Employing NPs for drug delivery safeguards the drugs from metabolic processes and enhances the effective transportation of poorly soluble drugs to specific target cells [38]. For example, research discovered that when Dalargin was orally given in the form of PS80-coated PACA nanoparticles, it was able to traverse the BBB and produce a pain-relieving impact [56]. NPs have been utilized as efficient agents for delivering drugs in the management of MPS, a set of hereditary metabolic disorders characterized by impaired functioning of lysosomal enzymes responsible for breaking down GAGs. A recent investigation employing PLGA nanoparticles in conjunction with simil, an opioid g7, demonstrated their capability to be directed towards particular brain cells. This was achieved through intraperitoneal and oral administration, indicating their effectiveness in conveying therapeutic enzymes across the BBB [57]. An additional illustration could involve PBCA nanoparticles, which have effectively been employed to transport practical proteins into both neurons and cell lines associated with neurons [58].

3.4 SLN

An alternative category of nanoparticles used as efficient vehicles for drug delivery are SLNs. These colloidal nanocarriers, comprising natural lipids (steroids, fatty acids, triglycerides, and waxes), are dispersed in water or a surfactant solution. Upon cooling, SLNs have the ability to solidify [39]. Much like NPs, the incorporation of PEG into SLNs enhances their ability to penetrate the BBB and improve the transport of drugs to the CNS. For example, research revealed that PEG-modified SLNs efficiently carry anticancer medications like camptothecin and doxorubicin [59]. SLNs offer various benefits compared to NPs. These advantages include minimal cytotoxicity, structural stability, and safeguarding fragile drugs against deterioration. Moreover, SLNs facilitate the transportation of therapies to the brain and allow for regulated drug release [39]. Several accounts indicate an improved method of delivering drugs to the brain facilitated by SLNs. To illustrate, when an SLN loaded with a calcium channel blocking drug was intravenously administered to rodents, it exhibited more efficient brain uptake and sustained elevated drug concentrations compared to a freely suspended drug.

3.5 Dendrimers

Dendrimers are complex, water-soluble artificial macromolecules distinguished by their homogeneity, three-dimensional spherical shapes, large branching points, and nanometer-scale dimensions.

Dendrimers possess distinctive characteristics, such as uniform molecular weight devoid of specific weight variation, a three-dimensional structure, reduced hydrodynamic volume, and smaller molecular dimensions in comparison to linear polymers of comparable molecular weight. The arrangement of dendrimers with developed generations offers a promising potential for a diverse range of uses, including the encapsulation of drugs [60]. Utilizing dendrimers as systems for delivering drugs offers numerous benefits, including extended duration of the drug within the bloodstream, shielding the drug from its surroundings, enhanced permanency of the active substance, and targeted delivery to specific tissues [61]. Different categories of dendrimers, including PAMAM, polyhydroxylamine, PLL, and PPI have been employed for transporting drugs

and contrast factors [62]. Dendrimer-centric approaches for delivering drugs can be harnessed for directing drugs to the brain, employing both invasive and non-invasive techniques [63]. Among these approaches, CMT emerges as particularly encouraging. For instance, Sharma and colleagues [64] successfully attached mannose molecules to the outside of fourth-generation PAMAM dendrimers furnished with terminal hydroxyl groups via click chemistry. This investigation aimed to determine whether binding target ligands could enhance the uptake of substances within the brain. The findings from in vitro tests demonstrated that the alteration involving mannose brought about a notable shift in the internalization process of dendrimers. This modification made them more inclined to undertake mannose-mediated endocytosis through carriers. Crucially, the researchers observed that the attachment of mannose to PAMAM dendrimers induced an altered dispersion pattern of dendrimers within the neonatal rabbit cerebral palsy model. Remarkably, this alteration did not lead to a reduction in the quantity of dendrimers delivered to the damaged glial cells in the brain [64]. The transporters CAT1, LAT1, GLUT1, choline transporter, and nucleobase transporter can also be used to transport dendrimer-linked conjugates. Dendrimer-centered systems for drug delivery can also navigate the BBB through mechanisms like AMT and RMT [63].

3.6 Polymeric micelles

Polymeric micelles represent an alternative kind of drug delivery system that self-assembles naturally within solutions containing amphiphilic copolymers. They adopt a structure characterized by a shell-core arrangement. In essence, polymeric micelles comprise a hydrophobic block polymer such as L,D-lactide polycaprolactone forming the core and a hydrophilic block polymer like PEGs forming the outer shell. Typically falling within the range of 10 to 100 nm in size, these nanoscale devices are designed to transport drugs that are not soluble in water [38]. In addition to improving the stability of drugs and bioavailability, polymeric micelles also protect therapeutic compounds from interactions with blood proteins. These attributes collectively render polymeric micelles well-suited for precise drug delivery to the brain. For instance, Ding and colleagues [65] documented the creation of dual-component polymeric micelles, comprising PEG copolymers integrated with borneol, designed for the specific conveyance of vinpocetine. These arrangements facilitated extended drug release in vitro and elevated drug levels within the brain.

3.7 CNTs

CNTs have recently become a promising substrate for nanocarriers, consisting of nano-sized cylinders formed from graphene sheets, for addressing diseases within the CNS. CNTs hold significant potential due to their capacity for surface customization through targeted chemical modifications that can influence both their physical and biological attributes [66]. As an example, chemically modified MWCNTs possess the capability to readily traverse the BBB, resulting in improved accumulation of CNTs within tumor locations [62]. However, the application of CNTs carries significant drawbacks, including substantial potential for unfavorable reactions, toxicity concerns, inconsistency between different batches, and a notably expensive production process [67]. In the study by Lohan and colleagues [68], They talked of adding berberine, an isoquinoline alkaloid, to the phospholipid-coated MWCNTs' surface. These nanoscale constructs played a role in restoring memory in rats afflicted with AD following administration from the 18th to the 20^th day. Pharmacokinetic investigations demonstrated notable enhancements in the speed and scope of berberine assimilation into both the bloodstream and brain, suggesting that these MWCNTs traverse the BBB. Consequently, the researchers hypothesized that the engineered nanoformulation holds substantial promise for mitigating the aggregation of β-amyloid [68].

4 SUMMARY AND FUTURE DIRECTIONS

Targeting the brain remains a formidable challenge. Overcoming a range of barriers such as structural, chemical, transport-related (physiological), and metabolic obstacles is essential for effectively treating different CNS disorders. In recent decades, there has been a focus on creating and deploying devices for delivering drugs to the brain with precision. This has garnered the interest of researchers and led to significant advancements in this area. As a result, we have witnessed notable advancements in the field. These include innovative drug delivery approaches that go beyond conventional treatments for various central nervous system disorders like epilepsy, stroke, brain cancer, and traumatic brain injury. Significantly, advancements in comprehending the structure and functioning of the BBB under both normal and pathological conditions have led to a growing acknowledgment of the difficulties in delivering drugs for brain disorders. In order to create effective new targeted drug delivery methods, it is imperative to possess an understanding of the roles played by various brain cell elements, including microglia, astrocytes, and endothelial cells, in the pathology of central nervous system diseases.

The challenges in achieving drug delivery to the brain specifically encompass several factors:

1. The limited predictive accuracy of preclinical models,
2. An incomplete grasp of brain disease mechanisms,
3. The absence of dependable pharmacodynamic biomarkers,
4. Imprecise assessment methods for clinical outcomes,

5. Considerable diversity within the clinical population.

Achieving therapeutic levels of drugs in brain tissue is a challenge for most substances after they are administered intravenously or orally. As a result, invasive methods are often employed to address this issue. Various invasive approaches enable the direct delivery of drugs to brain tissue. Furthermore, alternative techniques have been devised, including approaches that involve compromising the integrity of the blood-brain barrier through biochemical or osmotic means. Additionally, the utilization of biodegradable delivery systems has also been explored. Nevertheless, employing these approaches comes with various limitations, such as subjecting patients to physiological stress, raising intracranial pressure, or inadvertently delivering anticancer drugs to healthy areas of the brain. Certain techniques, like intrathecal injections, also exhibit drawbacks due to their sluggish and insufficient diffusion within the brain. Furthermore, incorrect catheter positioning can result in stark bleeding or encephalitis. On the other hand, techniques like intracerebral implants have presented improved remedies for precise drug delivery to the brain. These implants not only safeguard therapeutic agents from degradation but also regulate localized release, resulting in reduced systemic adverse effects. Numerous preclinical investigations have indicated encouraging effectiveness of drug delivery systems based on nanotechnology. Nonetheless, the transition from laboratory findings to practical clinical applications is challenging due to limited understanding regarding toxicity, which remains not entirely established, as well as concerns encompassing aggregation and swift elimination. Hence, conducting comprehensive toxicology evaluations and establishing the pharmacokinetic characteristics of brain-targeting nanostructures is entirely warranted. Researchers suggest that not only degradation byproducts but also biocompatibility need to be thoroughly scrutinized. Consequently, forthcoming findings from more advanced investigations into enhancing existing nano-sized drug delivery systems will undoubtedly unveil the therapeutic capabilities of nanomedicine for delivering drugs to the brain. During the evolution of CNS medications, the BBB poses a significant obstacle, impeding numerous pharmaceutical compounds from penetrating the brain to exert their intended biological actions. As a result, effectively treating individuals afflicted with conditions like epilepsy, neurodegenerative ailments, and brain tumors is notably complex. Nevertheless, as research into CNS and BBB physiology continually expands, there is an optimistic outlook for overcoming the challenges posed by CNS disorders in the times ahead. As a rule, only a limited selection of nutrients and peptides can easily traverse the BBB to attain sufficient concentrations in the brain following oral or intravenous dosing. In certain instances, it might be imperative to disturb the BBB's integrity or directly introduce therapeutics into brain tissue using various methods at hand, such as convection-enhanced delivery, intracerebral implants, or intraventricular administration. The primary obstacle confronting medicinal chemists, neurologists, and technologists is to achieve the ideal drug concentration within brain tissue. Nanotechnology, especially nanomedicine, offers a potential solution by enabling the creation of efficient and secure nanocarriers. These nanocarriers can deliver an appropriate quantity of therapeutic substances while minimizing systemic adverse effects. Modern nanotechnology encompasses an array of nanocarriers, such as micelles, polymeric nanoparticles, nanoemulsions, liposomes, and dendrimers, which are progressively gaining significant scientific interest for their diagnostic and therapeutic roles. Additional enhancements to these nanocarriers will enable improved compatibility of drugs within the body and extend their time in circulation, all the while diminishing their adverse effects on the entire system. Precision chemotherapy and antisense gene treatment for malignant brain tumors were made possible by nanoscale drug delivery elements, resulting in significant disease suppression in both laboratory settings and living organisms. Nonetheless, only a handful of encouraging preclinical investigations have transitioned effectively into clinical application. We hold the view that the potential of employing nanomedicine for CNS drug delivery is highly auspicious. However, more extensive research is required to comprehensively evaluate its impact on the human physiology.

ABBREVIATIONS

CNS: central nervous system, AD: Alzheimer's disease
PD: Parkinson's disease, MS: multiple sclerosis
BBB: Blood-Brain Barrier, EC: endothelial cell
FFA: free fatty acids, BCSF: blood-cerebrospinal fluid
CMT: carrier-mediated transport, RMT: receptor-mediated transport
AME: adsorptive-mediated endocytosis, CSF: cerebrospinal fluid
VIP: vasoactive intestinal peptide, PEG: polyethylene glycol
PCL: polycaprolactone, CPP: cell-penetrating peptide
TfR: transferrin receptor, PIL: PEGylated immunoliposome
MAb: monoclonal antibody, CED: convection-enhanced delivery
IA: intraarterial, MSC: mesenchymal stem cells
AIS: ischemic stroke, RES: resveratrol
RES NP: polymeric nanoparticle, LAO: large artery occlusion
FDA: Food and Drug Administration, CSF: cerebrospinal fluid
ICV: intracerebroventricular, FGF: fibroblast growth factor
MRI: magnetic resonance imaging, AAV: Adeno-Associated Virus
LSD: lysosomal storage disease, DRG: dorsal root ganglion
FUS: focused ultrasound, GBM: glioblastoma multiforme
PET: positron emission tomography, CED: Convection enhanced delivery
LDL: low-density lipoprotein, GLUT1: glucose transporter 1
LAT1: L -type amino acid transporter 1, PVA: polyvinyl alcohol
BBTB: blood-brain-tumor barrier, EV: Extracellular vesicles
MVB: multivesicular bodie, ILV: intraluminal vesicle
miRNA: microRNA, NP: Polymeric nanoparticle
PACA: poly alkylcyanoacrylate, PLA: poly lactide
PLGA: poly D,L-lactide-coglycolic acid, MPS mucopolysaccharidoses
GAG: glycosaminoglycans, PBCA: polybutylcyanoacrylate
SLN: solid-lipid nanoparticle, PAMAM: polyamidoamine

PLL: poly-L-lysine, PPI: polypropylene amine
CMT: carrier-mediated transport, CAT1: cationic amino acid transporter 1
AMT: adsorptive-mediated transcytosis, CNT: Carbon nanotube
MWCNT: multiwalled carbon nanotube

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Financing: The study was performed without external funding.
Ethical consideration: The study was approved by University of Anbar, Anbar, Iraq.
Data Availability: No data was used for the research described in the article.

REFERENCES

[1] Johanson CE, Johanson NL. Choroid plexus blood-CSF barrier: major player in brain disease modeling and neuromedicine. Journal of Neurology & Neuromedicine. 2018;3(4). doi:10.29245/2572.942X/2018/4.1194.

[2] Dong X. Current strategies for brain drug delivery. Theranostics. 2018;8(6):1481. doi:10.7150/thno.21254.

[3] Chen Y, Liu L. Modern methods for delivery of drugs across the blood–brain barrier. Advanced drug delivery reviews. 2012;64(7):640-65. doi:10.1016/j.addr.2011.11.010.

[4] Masereeuw R, Jaehde U, Langemeijer MW, de Boer AG, Breimer DD. In vitro and in vivo transport of zidovudine (AZT) across the blood–brain barrier and the effect of transport inhibitors. Pharmaceutical research. 1994;11:324-30. doi:10.1023/a:1018932213953.

[5] Rautio J, Laine K, Gynther M, Savolainen J. Prodrug approaches for CNS delivery. The AAPS journal. 2008;10:92-102. doi:https://doi.org/10.1208/s12248-008-9009-8.

[6] Markowicz-Piasecka M, Markiewicz A, Darłak P, Sikora J, Adla SK, Bagina S, et al. Current chemical, biological, and physiological views in the development of successful brain-targeted pharmaceutics. Neurotherapeutics. 2022;19(3):942-76. doi:10.1007/s13311-022-01228-5.

[7] Sharma U, Badyal PN, Gupta S. Polymeric nanoparticles drug delivery to brain: A review. Int J Pharmacol. 2015;2(5):60-9.

[8] Kasinathan N, Jagani HV, Alex AT, Volety SM, Rao JV. Strategies for drug delivery to the central nervous system by systemic route. Drug delivery. 2015;22(3):243-57. doi:10.3109/10717544.2013.878858.

[9] Lu CT, Zhao YZ, Wong HL, Cai J, Peng L, Tian XQ. Current approaches to enhance CNS delivery of drugs across the brain barriers. International journal of nanomedicine. 2014:2241-57.

[10] Soni S, Ruhela RK, Medhi B. Nanomedicine in central nervous system (CNS) disorders: a present and future prospective. Advanced pharmaceutical bulletin. 2016;6(3):319. doi:10.15171%2Fapb.2016.044.

[11] Li J, Ai Y, Wang L, Bu P, Sharkey CC, Wu Q, et al. Targeted drug delivery to circulating tumor cells via platelet membrane-functionalized particles. Biomaterials. 2016;76:52-65. doi:10.1016/j.biomaterials.2015.10.046.

[12] Blömer U, Ganser A, Scherr M. Invasive drug delivery. Molecular and Cellular Biology of Neuroprotection in the CNS. 2002:431-51. doi:10.1007/978-1-4615-0123-7_16.

[13] Haumann R, Videira JC, Kaspers GJ, van Vuurden DG, Hulleman E. Overview of current drug delivery methods across the blood–brain barrier for the treatment of primary brain tumors. CNS drugs. 2020;34(11):1121-31. doi:10.1007/s40263-020-00766-w.

[14] Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain research bulletin. 2018;143:155-70. doi:10.1016/j.brainresbull.2018.10.009.

[15] Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Advanced drug delivery reviews. 2012;64(7):614-28. doi:10.1016/j.addr.2011.11.002.

[16] Dufes C, Olivier JC, Gaillard F, Gaillard A, Couet W, Muller JM. Brain delivery of vasoactive intestinal peptide (VIP) following nasal administration to rats. International journal of pharmaceutics. 2003;255(1-2):87-97. doi:10.1016/s0378-5173(03)00039-5.

[17] Kanazawa T, Akiyama F, Kakizaki S, Takashima Y, Seta Y. Delivery of siRNA to the brain using a combination of nose-to-brain delivery and cell-penetrating peptide-modified nano-micelles. Biomaterials. 2013;34(36):9220-6. doi:10.1016/j.biomaterials.2013.08.036.

[18] Katare YK, Piazza JE, Bhandari J, Daya RP, Akilan K, Simpson MJ, et al. Intranasal delivery of antipsychotic drugs. Schizophrenia research. 2017;184:2-13. doi:10.1016/j.schres.2016.11.027.

[19] Huang R, Boltze J, Li S. Strategies for improved intra-arterial treatments targeting brain tumors: a systematic review. Frontiers in Oncology. 2020;10:1443. doi:10.3389/fonc.2020.01443.

[20] D'Amico RS, Khatri D, Reichman N, Patel NV, Wong T, Fralin SR, et al. Super selective intra-arterial

cerebral infusion of modern chemotherapeutics after blood–brain barrier disruption: Where are we now, and where we are going. Journal of neuro-oncology. 2020;147:261-78. doi:10.1007/s11060-020-03435-6.

[21] Blakeley J. Drug delivery to brain tumors. Current neurology and neuroscience reports. 2008;8:235-41. doi:10.1007/s11910-008-0036-8.

[22] Watanabe M, Yavagal DR. Intra-arterial delivery of mesenchymal stem cells. Brain circulation. 2016;2(3):114. doi:10.4103%2F2394-8108.192522.

[23] Lu X, Dong J, Zheng D, Li X, Ding D, Xu H. Reperfusion combined with intraarterial administration of resveratrol-loaded nanoparticles improved cerebral ischemia–reperfusion injury in rats. Nanomedicine: Nanotechnology, Biology and Medicine. 2020;28:102208. doi:10.1016/j.nano.2020.102208.

[24] René CA, Parks RJ. Delivery of therapeutic agents to the central nervous system and the promise of extracellular vesicles. Pharmaceutics. 2021;13(4):492. doi:10.3390/pharmaceutics13040492.

[25] Hocquemiller M, Giersch L, Audrain M, Parker S, Cartier N. Adeno-associated virus-based gene therapy for CNS diseases. Human gene therapy. 2016;27(7):478-96. doi:10.1089/hum.2016.087.

[26] Hudry E, Vandenberghe LH. Therapeutic AAV gene transfer to the nervous system: a clinical reality. Neuron. 2019;101(5):839-62. doi:10.1016/j.neuron.2019.02.017.

[27] Gray SJ, Woodard KT, Samulski RJ. Viral vectors and delivery strategies for CNS gene therapy. Therapeutic delivery. 2010;1(4):517-34. doi:10.4155/tde.10.50.

[28] Perez BA, Shutterly A, Chan YK, Byrne BJ, Corti M. Management of neuroinflammatory responses to AAV-mediated gene therapies for neurodegenerative diseases. Brain Sciences. 2020;10(2):119. doi:10.3390/brainsci10020119.

[29] Rich MC, Sherwood J, Bartley AF, Whitsitt QA, Lee M, Willoughby W, et al. Focused ultrasound blood brain barrier opening mediated delivery of MRI-visible albumin nanoclusters to the rat brain for localized drug delivery with temporal control. Journal of Controlled Release. 2020;324:172-80. doi:10.1016/j.jconrel.2020.04.054.

[30] Arif WM, Elsinga PH, Gasca-Salas C, Versluis M, Martínez-Fernández R, Dierckx RA, et al. Focused ultrasound for opening blood-brain barrier and drug delivery monitored with positron emission tomography. Journal of controlled release. 2020;324:303-16. doi:10.1016/j.jconrel.2020.05.020.

[31] Hynynen K. Ultrasound for drug and gene delivery to the brain. Advanced drug delivery reviews. 2008;60(10):1209-17. doi:10.1016/j.addr.2008.03.010.

[32] Olsman M, Sereti V, Andreassen K, Snipstad S, van Wamel A, Eliasen R, et al. Ultrasound-mediated delivery enhances therapeutic efficacy of MMP sensitive liposomes. Journal of controlled release. 2020;325:121-34. doi:10.1016/j.jconrel.2020.06.024.

[33] Markowicz-Piasecka M, Darłak P, Markiewicz A, Sikora J, Adla SK, Bagina S, et al. Current approaches to facilitate improved drug delivery to the central nervous system. European Journal of Pharmaceutics and Biopharmaceutics. 2022;181:249-62. doi:10.1016/j.ejpb.2022.11.003.

[34] Poon C, McMahon D, Hynynen K. Noninvasive and targeted delivery of therapeutics to the brain using focused ultrasound. Neuropharmacology. 2017;120:20-37. doi:10.1016/j.neuropharm.2016.02.014.

[35] Faraji AH, Rajendran S, Jaquins-Gerstl AS, Hayes HJ, Richardson RM. Convection-enhanced delivery and principles of extracellular transport in the brain. World Neurosurgery. 2021;151:163-71. doi:10.1016/j.wneu.2021.05.050.

[36] Brown CB, Jacobs S, Johnson MP, Southerland C, Threatt S. Convection-enhanced delivery in the treatment of glioblastoma. In: Seminars in Oncology Nursing. vol. 34. Elsevier; 2018. p. 494-500. doi:10.1016/j.soncn.2018.10.004.

[37] White E, Bienemann A, Taylor H, Hopkins K, Cameron A, Gill S. A phase I trial of carboplatin administered by convection-enhanced delivery to patients with recurrent/progressive glioblastoma multiforme. Contemporary clinical trials. 2012;33(2):320-31. doi:10.1016/j.cct.2011.10.010.

[38] Saeedi M, Eslamifar M, Khezri K, Dizaj SM. Applications of nanotechnology in drug delivery to the central nervous system. Biomedicine & pharmacotherapy. 2019;111:666-75. doi:10.1016/j.biopha.2018.12.133.

[39] Naqvi S, Panghal A, Flora S. Nanotechnology: a promising approach for delivery of neuroprotective drugs. Frontiers in Neuroscience. 2020;14:494. doi:10.3389/fnins.2020.00494.

[40] Ribovski L, Hamelmann NM, Paulusse JM. Polymeric nanoparticles properties and brain delivery. Pharmaceutics. 2021;13(12):2045. doi:10.3390/pharmaceutics13122045.

[41] Kong SD, Lee J, Ramachandran S, Eliceiri BP, Shubayev VI, Lal R, et al. Magnetic targeting of nanoparticles across the intact blood–brain barrier. Journal of controlled release. 2012;164(1):49-57. doi:10.1016/j.jconrel.2012.09.021.

[42] Yemisci M, Caban S, Gursoy-Ozdemir Y, Lule S, Novoa-Carballal R, Riguera R, et al. Systemically administered brain-targeted nanoparticles transport peptides across the blood—brain barrier and provide neuroprotection. Journal of Cerebral Blood Flow & Metabolism. 2015;35(3):469-75. doi:10.1038/jcbfm.2014.220.

[43] Song Q, Huang M, Yao L, Wang X, Gu X, Chen J, et al. Lipoprotein-based nanoparticles rescue the memory loss of mice with Alzheimer's disease by accelerating the clearance of amyloid-beta. ACS nano. 2014;8(3):2345-59. doi:10.1021/nn4058215.

[44] Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood–brain barrier to treat neurodegenerative diseases. Journal of controlled release. 2016;235:34-47. doi:10.1016/j.jconrel.2016.05.044.

[45] Jiang X, Xin H, Ren Q, Gu J, Zhu L, Du F, et al. Nanoparticles of 2-deoxy-D-glucose functionalized poly (ethylene glycol)-co-poly (trimethylene carbonate) for dual-targeted drug delivery in glioma treatment. Biomaterials. 2014;35(1):518-29. doi:10.1016/j.biomaterials.2013.09.094.

[46] Bahadur S, Naurange T, Baghel P, Sahu M, Yadu K. Targeting the brain: various approaches and science involved. ScienceRise: Pharmaceutical Science. 2020;(5 (27)):4-16. doi:10.15587/2519-4852.2020.210824.

[47] Spuch C, Navarro C. Liposomes for targeted delivery of active agents against neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Journal of drug delivery. 2011;2011. doi:10.1155/2011/469679.

[48] Fiandaca MS, Berger MS, Bankiewicz KS. The use of convection-enhanced delivery with liposomal toxins in neurooncology. Toxins. 2011;3(4):369-97. doi:10.3390/toxins3040369.

[49] Patel MM, Patel BM. Crossing the blood–brain barrier: recent advances in drug delivery to the brain. CNS drugs. 2017;31:109-33. doi:https://doi.org/10.1007/s40263-016-0405-9.

[50] Zheng M, Huang M, Ma X, Chen H, Gao X. Harnessing exosomes for the development of brain drug delivery systems. Bioconjugate Chemistry. 2019;30(4):994-1005. doi:10.1021/acs.bioconjchem.9b00085.

[51] Didiot MC, Hall LM, Coles AH, Haraszti RA, Godinho BM, Chase K, et al. Exosome-mediated delivery of hydrophobically modified siRNA for huntingtin mRNA silencing. Molecular Therapy. 2016;24(10):1836-47. doi:10.1038/mt.2016.126.

[52] Den Hartogh DJ, Gabriel A, Tsiani E. Antidiabetic properties of curcumin I: Evidence from in vitro studies. Nutrients. 2020;12(1):118. doi:10.3390/nu12010118.

[53] Sun D, Zhuang X, Xiang X, Liu Y, Zhang S, Liu C, et al. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Molecular therapy. 2010;18(9):1606-14. doi:10.1038/mt.2010.105.

[54] Qu M, Lin Q, Huang L, Fu Y, Wang L, He S, et al. Dopamine-loaded blood exosomes targeted to brain for better treatment of Parkinson's disease. Journal of controlled release. 2018;287:156-66. doi:10.1016/j.jconrel.2018.08.035.

[55] Zhao Y, Haney MJ, Gupta R, Bohnsack JP, He Z, Kabanov AV, et al. GDNF-transfected macrophages produce potent neuroprotective effects in Parkinson's disease mouse model. PloS one. 2014;9(9):e106867. doi:10.1371/journal.pone.0106867.

[56] Das D, Lin S. Double-coated poly (butylcynanoacrylate) nanoparticulate delivery systems for brain targeting of dalargin via oral administration. Journal of pharmaceutical sciences. 2005;94(6):1343-53. doi:10.1002/jps.20357.

[57] Bellettato CM, Scarpa M. Possible strategies to cross the blood–brain barrier. Italian journal of pediatrics. 2018;44(2):127-33. doi:10.1186/s13052-018-0563-0.

[58] Masserini M. Nanoparticles for brain drug delivery. International Scholarly Research Notices. 2013;2013. doi:10.1155/2013/238428.

[59] Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid lipid nanoparticles for targeted brain drug delivery. Advanced drug delivery reviews. 2007;59(6):454-77. doi:10.1016/j.addr.2007.04.011.

[60] Markowicz-Piasecka M, Mikiciuk-Olasik E. Dendrimers in drug delivery. In: Nanobiomaterials in Drug Delivery. Elsevier; 2016. p. 39-74. doi:10.1016/B978-0-323-42866-8.00002-2.

[61] Chauhan AS. Dendrimers for drug delivery. Molecules. 2018;23(4):938. doi:10.3390/molecules23040938.

[62] Ma X, Zhong L, Guo H, Wang Y, Gong N, Wang Y, et al. Multiwalled carbon nanotubes induced hypotension by regulating the central nervous system. Advanced Functional Materials. 2018;28(11):1705479. doi:10.1002/adfm.201705479.

[63] Zhu Y, Liu C, Pang Z. Dendrimer-based drug delivery systems for brain targeting. Biomolecules. 2019;9(12):790. doi:10.3390/biom9120790.

[64] Sharma A, Porterfield JE, Smith E, Sharma R, Kannan S, Kannan RM. Effect of mannose targeting of hydroxyl PAMAM dendrimers on cellular and organ biodistribution in a neonatal brain injury

model. Journal of Controlled Release. 2018;283:175-89. doi:10.1016/j.jconrel.2018.06.003.

[65] Ding J, Sun Y, Li J, Wang H, Mao S. Enhanced blood–brain barrier transport of vinpocetine by oral delivery of mixed micelles in combination with a message guider. Journal of drug targeting. 2017;25(6):532-40. doi:10.1080/1061186X.2017.1289541.

[66] Ahlawat J, Guillama Barroso G, Masoudi Asil S, Alvarado M, Armendariz I, Bernal J, et al. Nanocarriers as potential drug delivery candidates for overcoming the blood–brain barrier: challenges and possibilities. Acs Omega. 2020;5(22):12583-95. doi:10.1021/acsomega.0c01592.

[67] Wolfram J, Zhu M, Yang Y, Shen J, Gentile E, Paolino D, et al. Safety of nanoparticles in medicine. Current drug targets. 2015;16(14):1671-81.

[68] Lohan S, Raza K, Mehta S, Bhatti GK, Saini S, Singh B. Anti-Alzheimer's potential of berberine using surface decorated multi-walled carbon nanotubes: a preclinical evidence. International journal of pharmaceutics. 2017;530(1-2):263-78. doi:10.1016/j.ijpharm.2017.07.080.

How to cite this article

Al-Hamadiny S.Q.; Salman R.I.; Al-Rawe A.M.; Nanocarriers and Beyond: Innovations in Overcoming Barriers for Effective CNS Drug Delivery. Trends in Pharmaceutical Biotechnology (TPB). 2023;1(1):34-47. doi: 10.57238/tpb.2023.144275.1003