Materials Chemistry Horizons

REVIEW

# Drug Delivery for Brains and Central Nervous System

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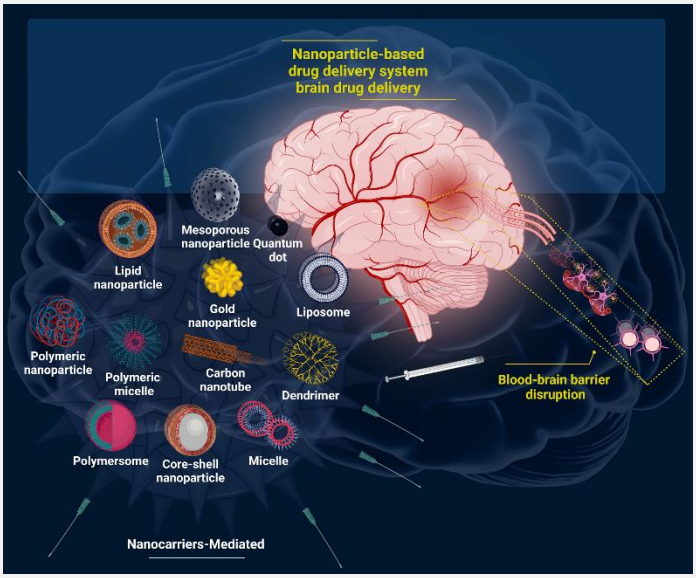
*Mater. Chem. Horizons*, 2023,2(4), 315-326 10.22128/mch.2024.765.1053 OPEN ACCESS

**ABSTRACT**

This comprehensive review delves into the intricate challenges and recent advancements in drug delivery to the central nervous system (CNS), with a primary focus on overcoming the formidable blood-brain barrier (BBB). The manuscript explores the protective barriers of crucial organs such as the skin, brain, and eyes, shedding light on the complexity of drug delivery systems. By emphasizing the significance of nanotechnology, particularly lipid nanoparticles, the study aims to provide a nuanced understanding of their unique properties and applications in CNS drug delivery. Various types of nanoparticles, including liposomes, cationic liposomes, solid lipid nanoparticles, gold nanoparticles, polymer nanoparticles, polymeric micelles, dendrimers, and mesoporous silica nanoparticles, are discussed in detail. The review further outlines strategies to enhance BBB permeation, such as transiently increasing permeability, diffusion of lipophilic molecules, and transcytosis pathways, offering a comprehensive overview of the evolving landscape of CNS drug delivery.




**Keywords:** Drug delivery, central nervous system, nanoparticles, liposomes, solid lipid nanoparticles

## 1. Introduction

The central nervous system (CNS), comprising the brain and spinal cord, plays a pivotal role in physiological functions, making it a critical target for therapeutic interventions. However, the protective nature of the blood-brain barrier (BBB) poses a significant challenge for effective drug delivery to the CNS [1-5].

Delivering drugs to the central nervous system (CNS) and brain is challenging due to the blood-brain barrier, which prevents most drugs from crossing from the bloodstream into the brain. Strategies have been developed to enhance drug delivery across the blood-brain barrier, including modification of the drug itself or using invasive delivery methods like convection-enhanced delivery. Convection-enhanced delivery involves inserting a catheter into the brain parenchyma and infusing the drug solution under a positive pressure gradient. This method allows for targeted drug delivery while bypassing the blood-brain barrier [6-9].

This perspective article aims to provide an overview of the challenges and recent advancements in drug delivery to the CNS. The study specifically aims to explore the protective barriers of critical organs, emphasizing the complexity of drug delivery systems. By focusing on nanotechnology, the review aims to dissect the unique properties of lipid nanoparticles and their applications in CNS drug delivery. Additionally, the manuscript aims to discuss various types of nanoparticles and their mechanisms, offering insights into strategies to enhance BBB permeation. Ultimately, the review seeks to contribute to the evolving landscape of CNS drug delivery, paving the way for innovative and effective therapeutic interventions.

Received: December 24, 2023
Received in revised: January 22, 2024
Accepted: January 22, 2024

## 2. Types of nanoparticles for drug delivery

The emergence of nanotechnology has revolutionized every aspect of our lives and the drug delivery industry is not an exception [10-15]. Unique properties can be achieved when nanoparticles get involved in drug delivery applications leading to an increase in the performance and effectiveness of various drugs. Among different nanoparticles, lipid nanoparticles have received the most attention due to their special properties [16-20]. These carriers have properties very similar to emulsions or nanoemulsions because they are a mixture of solid fats and liquid oils coated with emulsifiers dispersed in the aqueous medium. They inhibit the further accumulation of drug molecules and active compounds in the lipid structure. Liposomes are the first generation of nanoparticles for the drug delivery system. They are composed of vesicles with two layers of amphiphilic lipids that create an internal aqueous environment. Liposomal bilayer lipids are biocompatible and biodegradable lipids present in biomembranes. They are widely used for drug delivery to the brain, and treatment of cerebral ischemia and brain tumors [21-24].

Cationic liposomes are positively charged lipids that were created as the first transport carriers to deliver genetic material into the cell. The interaction between cationic lipids and nucleic acids leads to the formation of the lipoplex structure. Unlike liposomes, cationic liposomes undergo endocytosis through absorption and enter the endosome. In the acidic environment of the endosome, Dioleoyl phosphatidylethanolamine mixes with the endosome membrane, destabilizing it, and releasing the contents of the endosome. Thus, drugs can be transported into endothelial cells increasing their passage through the BBB and reaching the nerve cells [25].

Solid lipid nanoparticles are made of biocompatible lipids such as triglycerides fatty acids and waxes and can pass through endothelial cells due to their small size (about 40 to 200 nm). The ability to continuously release drugs is one of the advantages of these nanoparticles that increase drug delivery to the midbrain [26-28]. Among the metal nanoparticles used to deliver drugs to the brain, gold nanoparticles have a special place that can cross the blood-brain barrier due to their biocompatibility, low toxicity, and even the need for functionalization [29-33].

Particles made of plasmonic metals like gold and silver possess a specialized optical trait, identified as localized surface plasmon resonance (LSPR). This property emerges due to the confinement of light within these minute particles, prompting a synchronized vibration of the electrons in the free conduction band. This vibration influences the metal nanoparticles' emissive and absorptive qualities. Specifically, emissive decay is characterized by a pronounced scattering of visible light, whereas absorptive decay results in the conversion of light energy into heat. These complex optical characteristics have made such metal nanoparticles highly valuable for a range of uses in biological and medical fields.

Gold nanoparticles (AuNPs) play a crucial role in revolutionizing drug delivery to the central nervous system (CNS). Overcoming the formidable blood-brain barrier (BBB) is a major challenge in delivering therapeutics to the brain, and AuNPs have shown exceptional capabilities in this regard. Their nanoscale size facilitates efficient penetration through the BBB, allowing for widespread distribution within the CNS upon intravenous administration. The surface characteristics of AuNPs can be tailored through modifications, enhancing their biocompatibility and enabling specific interactions with biological entities. This surface functionalization is instrumental in achieving targeted drug delivery by attaching ligands that interact with receptors on the BBB or specific cells within the brain. Additionally, the plasmonic properties of gold nanoparticles, characterized by localized surface plasmon resonance (LSPR), contribute to their unique optical traits, making them valuable for diagnostic applications, including imaging techniques like fluorescence and photoacoustic imaging.

The mechanism of gold nanoparticles in CNS drug delivery involves intricate processes such as size-dependent clearance and surface modification for enhanced biocompatibility [34-37]. The ability of AuNPs to traverse biological barriers and accumulate in brain cells, including neurons, positions them as promising agents for drug delivery. Their intravenous administration results in efficient distribution within the CNS, impacting various cell types. Furthermore, the careful consideration of clearance mechanisms is crucial to ensure both the efficacy and safety of AuNPs in medical treatments. Ongoing research continues to explore and optimize the use of gold nanoparticles, harnessing their unique properties to advance drug delivery precision, targeting, and diagnostic capabilities for effective interventions in neurological disorders.

Intravenous administration of these nanoparticles has demonstrated their widespread distribution within the central nervous system (CNS), affecting various cell types including neurons, endothelial cells, and glial cells. For instance,

colloidal gold nanoparticles around 20 nm have been predominantly observed in neurons, while also being present in endothelial and glial cells. A similar distribution pattern is seen with 5 nm glucose-coated gold nanoparticles, which show presence in the cortex's neurons, nerve axons (both myelinated and unmyelinated), astrocytes, and other glial cells, often within mere minutes post-injection [38].

These nanoparticles predominantly accumulate in the cytoplasm of brain cells, with some also being detected in the nuclei, though the exact mechanism of this nuclear entry is yet to be fully understood. Their capacity to traverse the endothelial layers and disperse away from blood vessels, while minimizing accumulation in intercellular spaces, positions them as promising agents for CNS drug delivery. However, it is vital to monitor their concentrations to avoid toxicity in the CNS.

For their application in medical treatments to be both effective and safe, the clearance process of AuNPs is a critical aspect. Smaller nanoparticles are believed to be expelled through processes like vesicular or cytosolic exocytosis, and transcytosis across the endothelium, followed by renal elimination. In contrast, larger nanoparticles are likely to be ingested by the brain's phagocytic cells, such as perivascular macrophages and microglia, or drained away via the cerebrospinal fluid to either the cervical lymphatics or the venous sinuses. Understanding this delicate balance between efficient drug delivery and safe nanoparticle clearance is essential in leveraging the full potential of gold nanoparticles for the management and diagnosis of brain disorders. Polymer nanoparticles are usually between 60 and 200 nm in size, and the most popular of them are polyethylene glycol (PLA), polyglycolic acid (PGA), and Poly lactic-co-glycolic acid (PLGA). Despite the development of synthetic and semi-synthetic polymers, natural polymers such as chitosan are also employed [39-41].

Fornaguera et al. synthesized PLGA NPs containing loperamide. These nanoparticles were encapsulated in polysorbate 80 and functionalized with monoclonal antibodies. The results showed that these polymeric NPs effectively cross the blood-brain barrier [42]. Polymeric micelles are composed of amphiphilic copolymers that accumulate in an aqueous medium, resulting in the production of spherical structures with a hydrophilic coating and a highly stable hydrophobic core. The adjustability of polymer micelles allows them to respond to external stimuli such as ultrasound, temperature, light, acidity, etc., and as a result, the drug trapped in it can be released in a controlled manner [43].

Quantum dots (QDs) have emerged as valuable tools in drug delivery, particularly for targeting the brain. Their unique optical properties make them excellent imaging agents, allowing real-time tracking of drug delivery within the body. QDs can be engineered with specific ligands for targeted drug delivery to the brain, interacting selectively with receptors on the blood-brain barrier (BBB). This targeted approach enhances drug delivery precision, minimizing off-target effects. Additionally, QDs facilitate overcoming the BBB by surface modifications or encapsulating drugs that can cross the barrier efficiently. Their tunable properties enable sustained and controlled release of therapeutic agents, crucial for treating neurological disorders. Overall, quantum dots play a pivotal role in improving drug delivery to the brain, offering targeted precision, imaging capabilities, and controlled release.

In summary, quantum dots represent a promising avenue for advancing drug delivery to the brain. Their unique optical properties enable real-time tracking, while surface modifications allow for targeted delivery to specific brain regions. Overcoming the blood-brain barrier is a significant challenge, and quantum dots offer strategies to enhance transport efficiency. Moreover, their tunable properties enable controlled drug release, optimizing therapeutic effects. In the realm of neurological disorders, quantum dots hold immense potential to revolutionize drug delivery, providing a multifaceted approach that combines precision, imaging, and controlled release for more effective treatments.

Dendrimers are branched polymers. A dendrimer typically forms symmetrically around a nucleus and, when sufficiently expanded, often appears in water as a three-dimensional sphere. Polyamidoamine (PAMAM) is the best-known compound for dendrimer synthesis. They can carry drug molecules by receptors on their surface or encapsulate them in cavities between branches [44]. Today, research on mesoporous silica nanoparticles (MSNs) for medical purposes has grown exponentially and extraordinary advances have been made in the diagnosis, imaging, and treatment of neurodegenerative diseases. They have significant advantages with their regular porous structure: 1- Adjustable cavity size and morphology of MSNs that are suitable for loading different materials, 2- As a drug delivery system, modified surface of MSNs can release loaded materials in a controlled manner, 3- MSNs with their multifunctional features (magnetic and fluorescent), allow imaging and drug delivery at the same time [45]. **Figure 1**

shows the nanoparticles that have been reported for the delivery of neurodegenerative diseases and many other ailments.

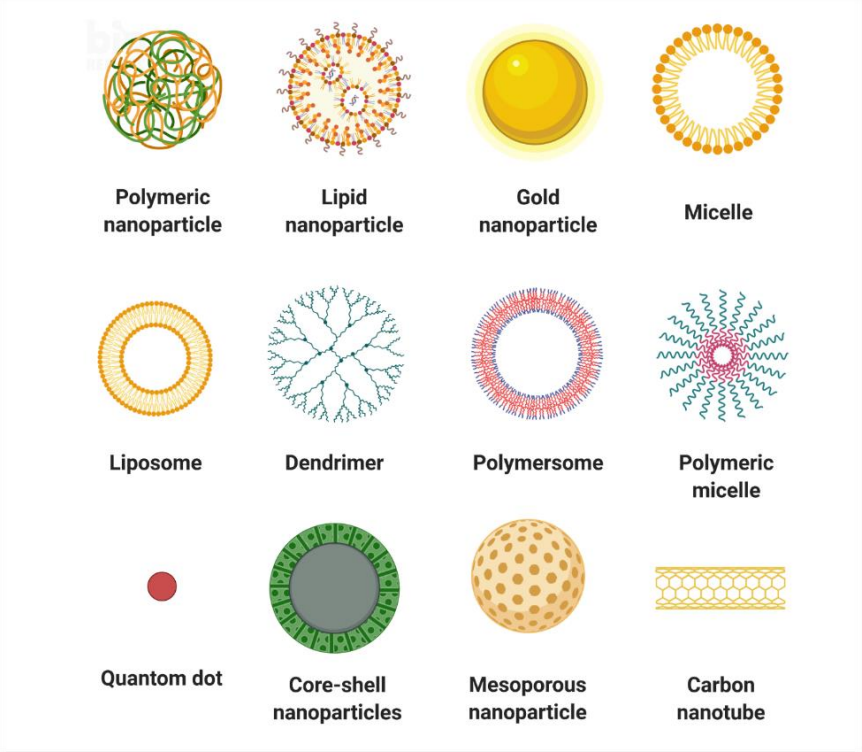



**Figure 1.** Schematic representation showing various kinds of nanoparticle-based drug delivery system brain drug delivery applications. Re-illustrated from [46] with permission from the American Chemical Society.

The central nervous system contains the brain and spinal cord, with the latter encased within the spine. A specialized barrier called the blood-brain barrier (BBB) separates the central nervous system from other bodily systems. The BBB consists of unique capillaries that lack the pores found in normal capillaries and have tightly connected cells (**Figure 2A**). Several strategies have been explored to enhance drug delivery across the BBB for treating brain diseases (**Figure 2B**) [46, 47]:

I. Transiently increasing BBB permeability using methods like ultrasound, microbubbles, and osmotic pressure changes. However, this allows uncontrolled nanoparticle entry and can disrupt brain homeostasis, causing toxicity.

II. Diffusion of small lipophilic molecules (<400 Da) through endothelial cells via paracellular and transcellular routes. Tight junctions block the passage of hydrophilic or insoluble drugs paracellularly. Lipid-based nanoparticles like liposomes and solid lipid nanoparticles can undergo transcellular passage by lipid-mediated diffusion or endocytosis given their lipid composition.

III. Transcytosis pathways involve adsorptive or receptor/carrier-mediated transport. Positively charged nanoparticles can adsorb to the negatively charged endothelial membrane and undergo absorptive transcytosis. Nanoparticles modified with targeting ligands can also exploit receptor-mediated endocytosis for transport. For instance, PEGylation of polylactide nanoparticles improved their BBB passage by adsorptive transcytosis in one study.

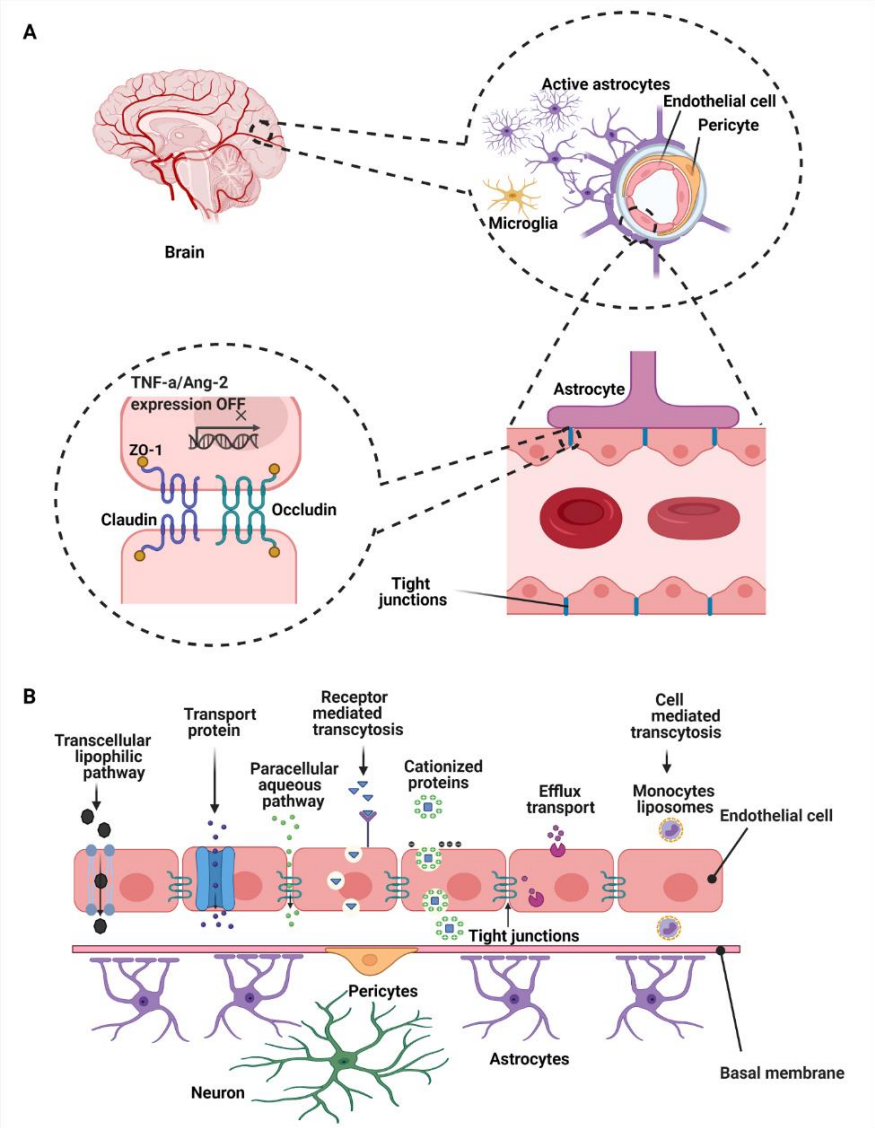



**Figure 2.** The blood-brain barrier (BBB). (A) Brain endothelial cells with tight junctions form the BBB and regulate transport between blood and the brain. Pericytes control blood flow while astrocytes support endothelial cells biochemically. (B) Strategies to enhance nanoparticle diffusion across the BBB include increasing BBB permeability, passive diffusion of lipophilic particles, and receptor-mediated transcytosis. Reprinted from [48] with permission from ACS.

## 3. Delivery to brains and central nervous system

The blood-brain barrier (BBB) is a major obstacle to delivering therapeutic agents to the central nervous system (CNS). The BBB is comprised of tightly joined capillary endothelial cells that prevent the passive diffusion of most drugs. Overcoming the BBB is a major challenge in developing treatments for neurological diseases and disorders. Strategies have been developed to transiently disrupt the BBB or utilize receptors to promote transcytosis. Nanotechnology has enabled the engineering of drug-delivery platforms capable of crossing the BBB through both paracellular and transcellular mechanisms [49-52].

Liposomes, nanoparticles, and nanocapsules have been extensively studied for CNS drug delivery. These nanocarriers can be designed to carry therapeutics across the BBB through receptor-mediated transport or adsorption to the cell surface followed by endocytosis. Surface functionalization with ligands targeting receptors like transferrin and insulin can promote receptor-mediated transcytosis. Poly(butyl cyanoacrylate) and poly(lactic-co-glycolic acid) nanoparticles in particular have shown promise in preclinical models. However, clinical translation remains limited to

date. Ongoing research is focused on increasing the drug-carrying capacity, targeting specificity, and transcytosis efficiency of nanocarriers to enhance their therapeutic delivery across the BBB [53-56].

In a study, Shadmani et al. [57] described the development of mesoporous silica nanoparticles (MSNs) functionalized with the cell-penetrating peptide TAT for enhanced delivery of the chemotherapy drug methotrexate (MTX) across the blood-brain barrier. The MSNs were synthesized using a sol-gel method and modified to have a particle size of around 50 nm (**Figure 3**). The MSNs were then conjugated with TAT peptide as a targeting ligand intended to improve transport into brain tissue. In vitro studies demonstrated pH-responsive release kinetics, with faster release at lower pH values mimicking the tumor microenvironment. *In vivo*, pharmacokinetic analysis in rats showed the TAT-functionalized MSNs (MSN-NH-TAT) increased the concentration of MTX in the brain parenchyma by 31-fold compared to free MTX. The brain uptake clearance of MSN-NH-TAT-MTX was 20-fold higher than free MTX. In cell studies, the MSN-NH-TAT-MTX formulation showed a 9-fold higher induction of apoptosis in glioma cells compared to free MTX after 8 hours of treatment. Overall, this study demonstrates that TAT-conjugated MSNs are a promising carrier system for enhanced chemotherapeutic delivery across the blood-brain barrier for potential treatment.

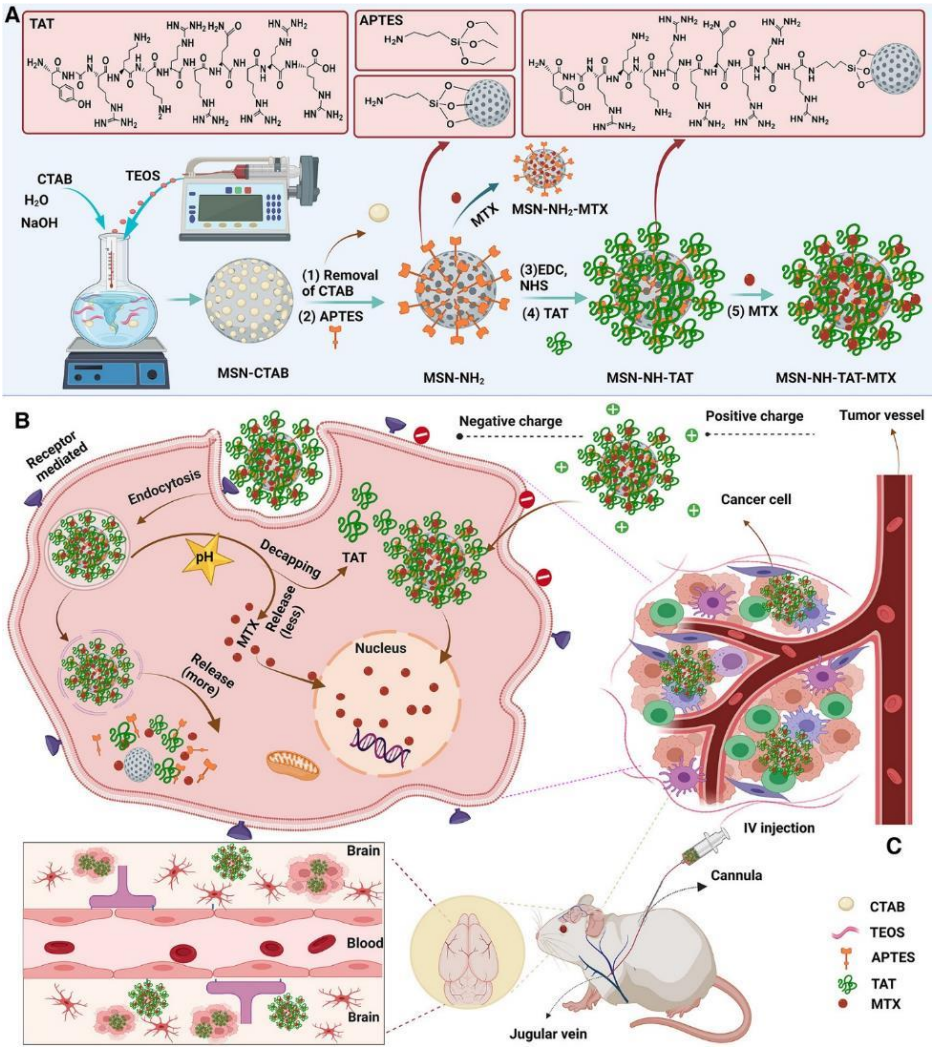



**Figure 3** Schematic presentation for fabrication and delivery application of silica nanoparticles for blood-brain barriers applications. Reprinted from [57] with permission from the American Chemical Society.

Alzheimer's disease, a prevalent neurodegenerative condition, is characterized by progressive cognitive decline and behavioral disturbances, primarily attributed to the deposition of amyloid β-protein (Aβ). Current therapeutic strategies have struggled to prevent neuronal loss induced by Aβ, necessitating innovative approaches [58, 59]. In a study by Wang and co-workers [8], a multifunctional nanosphere system incorporating double selenium (CLNDSe) was designed and prepared, and it was equipped with an A2AAR agonist (CGS) for targeted blood-brain barrier delivery, both in vitro and in vivo (**Figure 4**).

The modification with the LPFFD short peptide was utilized to facilitate the inhibition of Aβ42 aggregation and the mitigation of Aβ42-induced neural toxicity. This was achieved by suppressing oxidative damage and mitigating mitochondrial dysfunction. Furthermore, nerve growth factor (NGF) was introduced onto the larger selenium sphere, resulting in a significant reduction in Tau protein phosphorylation and the attenuation of gliocyte activation in APP/PS1 mice. The in vivo administration of CLNDSe nanoparticles effectively restored the antioxidant capacity of GPX1/4, and alleviated neural loss, neurofibrillary tangles, and neural ferroptosis, ultimately leading to the amelioration of cognitive deficits in APP/PS1 mice.

Notably, CLNDSe nanoparticles exhibited high safety and biocompatibility. The rational design of blood-brain barrier-targeted delivery of double selenium nanospheres has been validated as a promising strategy to alleviate Alzheimer's disease by inhibiting neural ferroptosis [8]. The developed double nanosphere system was able to deliver multiple drugs across the BBB. This system effectively transformed Aβ42 fibrils into Aβ42 oligomers and inhibited tau protein phosphorylation. The targeting of the BBB receptor facilitated rapid drug delivery to Aβ42 fibrils, resulting in significant therapeutic efficacy in APP/PS1 mouse models.

In contrast to current AD strategies based on nanoparticles, abnormal microglia outside Aβ42 fibrils or tau aggregates were primarily targeted by this system, thus reducing neuronal toxicity and ferroptosis. This approach held substantial clinical therapeutic potential. Moreover, leveraging the antioxidant properties of selenium and the synergistic effects of brain-specific drugs, the expression of ACSL4 and COX-2 proteins was downregulated, while FTH1, GPX1, and GPX4 were upregulated. This resulted in the effective elimination of intracellular and extracellular ROS in the Alzheimer's disease microenvironment, thereby inhibiting ferroptosis. This multi-target strategy aligned with the multi-cell interaction dynamics of Alzheimer's disease, offering greater control over the Alzheimer's disease microenvironment compared to other single-target systems. Furthermore, this ferroptosis-centric drug delivery system can be extended to address other neuroinflammatory-related diseases due to the pivotal role of neural cells in brain homeostasis [8].

**Table 1** compares different types of nanoparticles for central nervous system drug delivery. This table provides a brief overview of the advantages and challenges associated with each type of nanoparticle for CNS drug delivery, along with examples of each type. Keep in mind that the actual selection of nanoparticles for drug delivery depends on specific drug characteristics, target application, and the desired therapeutic outcomes. Additionally, ongoing research is addressing challenges and optimizing these nanoparticle systems for enhanced drug delivery efficacy. It's important to note that the suitability of nanoparticles for CNS drug delivery can vary based on the specific requirements of the drug, the targeted therapeutic effect, and the physiological conditions of the central nervous system. Additionally, ongoing research aims to address challenges associated with toxicity, stability, and scalability for each nanoparticle type.

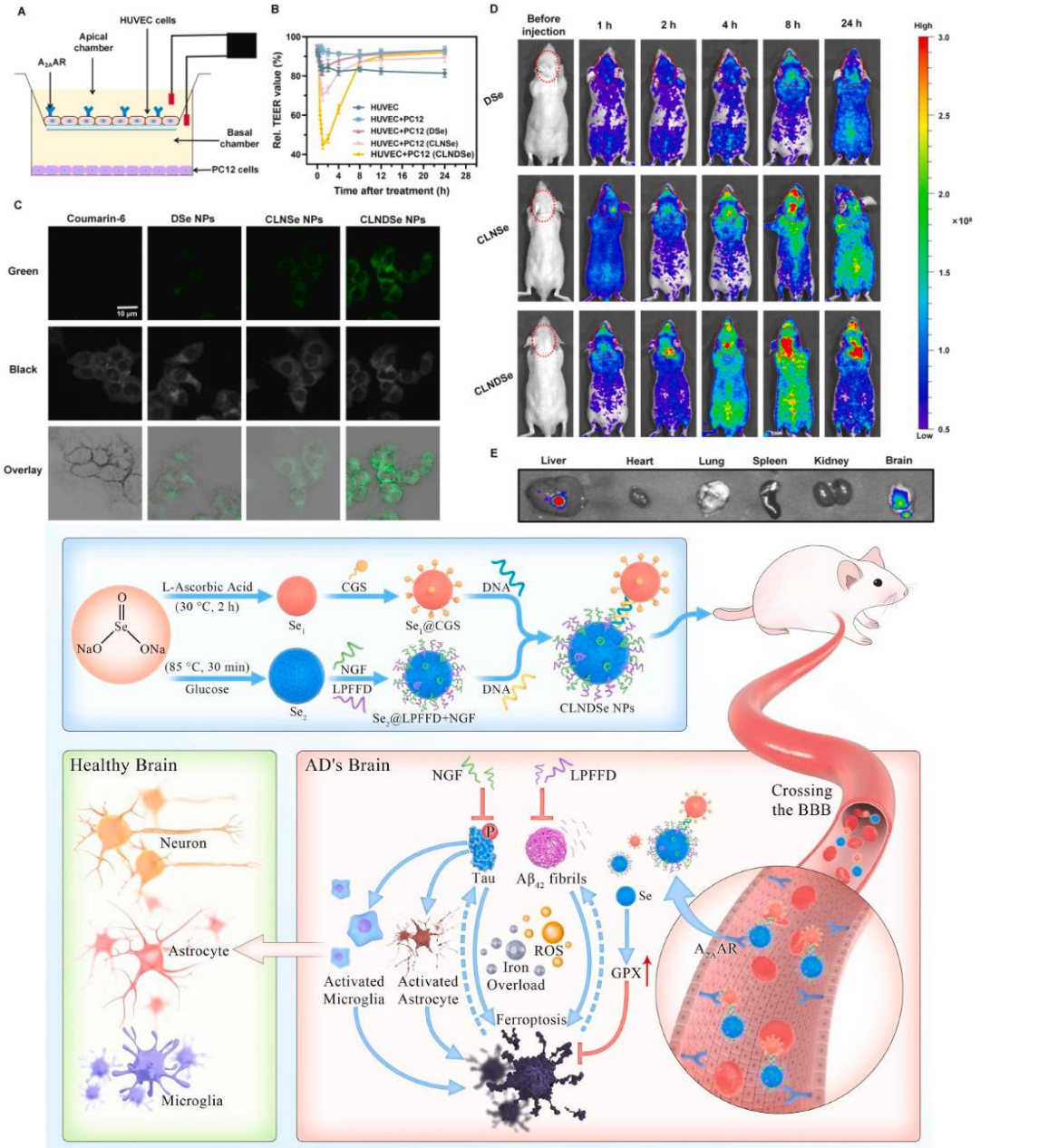



**Figure 4** (A) Schematic representation of the transwell assay and TEER measurement for evaluating co-cultured cell permeability. HUVEC cells are depicted in pink, PC12 cells in purple, A2AAR in blue, and electrode probes in red. (B) TEER values were measured immediately after nanoparticle addition (n = 6, mean ± SD). (C) In vivo imaging of NPs post-intravenous injection into APP/PS1 mice (n = 5). Brain regions are highlighted with red circles. (D) Fluorescence labeling of PC12 cells in the BBB model. (E) In vitro fluorescence imaging of dissected major organs. (F) Synthesis route and proposed signal pathway. Reprinted from [8] with permission from Elsevier.

**Table 1** different types of nanoparticles for central nervous system (CNS) drug delivery.

| Nanoparticle Type | Advantages | Challenges | Examples | References |
|---|---|---|---|---|
| Lipid Nanoparticles | - Biocompatible<br>- Versatile in drug encapsulation | - Limited payload capacity<br>- Potential instability | Liposomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs) | [60-62] |
| Polymeric Nanoparticles | Tailorable properties for drug release | -- Biocompatibility concerns | Poly(lactic-co-glycolic acid) (PLGA), Polymeric | [39, 63-65] |
| Gold Nanoparticles | - Sustained drug release<br>- Biocompatible, non-toxicity | - Difficulty in large-scale production<br>- Limited drug payload capacity | nanoparticles, Chitosan nanoparticles<br>Gold nanorods, Gold nanoshells, Gold nanocages | [66-68] |
| Magnetic Nanoparticles | - Responsive to external magnetic fields<br>- Facilitates targeted drug delivery | - Potential toxicity of magnetic materials<br>- Limited drug loading capacity | Iron oxide nanoparticles (Fe3O4, Fe2O3) | [69-71] |
| Quantum Dots | - Unique optical properties for imaging<br>- Potential for multifunctionality (imaging, targeting) | - Concerns about toxicity and long-term effects<br>- Clearance issues due to small size | Cadmium-based (CdSe, CdTe), Carbon-based (Carbon dots), Silicon-based (Si) quantum dots | [72-74] |

## 4. Conclusion and perspective

The primary aim of this review was to solve the complexities associated with CNS drug delivery, focusing on recent advancements and strategies to overcome the blood-brain barrier. The discussion begins by exploring the intricate barrier systems safeguarding vital organs, including the skin, brain, and eyes. By emphasizing the unique properties of nanotechnology, particularly lipid nanoparticles, the review aims to elucidate their potential in enhancing drug permeation through the blood-brain barrier Overall, the blood-brain barrier poses a major obstacle for delivering drugs to treat CNS diseases. Nanotechnology solutions like engineered lipid nanoparticles are enabling enhanced blood-brain barrier permeation through passive and active transport mechanisms.

In conclusion, nanoparticles, with their unique properties and diverse applications, hold promise in enhancing drug permeation through intricate barriers such as the blood-brain barrier. The exploration of various nanoparticle types and their mechanisms of action provides valuable insights into the evolving landscape of CNS drug delivery. As research in this field continues, nanotechnology remains a pivotal player in developing effective and targeted therapies for diseases affecting the central nervous system. The outlined strategies to enhance blood-brain barrier permeation offer avenues for future research and the development of clinically viable solutions for treating CNS disorders.

## Authors' contributions

All authors contributed to drafting, and revising the paper and agreed to be responsible for all the aspects of this work.

## Declaration of competing interest

The authors declare no competing interest.

## Funding

This paper received no external funding.

## Data availability

Not applicable.

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