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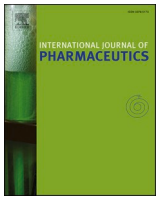

Review

Advancing neurological disorders therapies: Organic nanoparticles as a key to blood-brain barrier penetration

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ABSTRACT

The blood–brain barrier (BBB) plays a vital role in protecting the central nervous system (CNS) by preventing the entry of harmful pathogens from the bloodstream. However, this barrier also presents a significant obstacle when it comes to delivering drugs for the treatment of neurodegenerative diseases and brain cancer. Recent breakthroughs in nanotechnology have paved the way for the creation of a wide range of nanoparticles (NPs) that can serve as carriers for diagnosis and therapy. Regarding their promising properties, organic NPs have the potential to be used as effective carriers for drug delivery across the BBB based on recent advancements. These remarkable NPs have the ability to penetrate the BBB using various mechanisms. This review offers a comprehensive examination of the intricate structure and distinct properties of the BBB, emphasizing its crucial function in preserving brain balance and regulating the transport of ions and molecules. The disruption of the BBB in conditions such as stroke, Alzheimer's disease, and Parkinson's disease highlights the importance of developing creative approaches for delivering drugs. Through the encapsulation of therapeutic molecules and the precise targeting of transport processes in the brain vasculature, organic NP formulations present a hopeful strategy to improve drug transport across the BBB. We explore the changes in properties of the BBB in various pathological conditions and investigate the factors that affect the successful delivery of organic NPs into the brain. In addition, we explore the most promising delivery systems associated with NPs that have shown positive results in treating neurodegenerative and ischemic disorders. This review opens up new possibilities for nanotechnology-based therapies in cerebral diseases.

Abbreviations: Ach, Acetylcholine; AD, Alzheimer's Disease; AG, Andrographolide; ApoE, Apolipoprotein-E; Aβ, beta-amyloid; BBB, Blood-brain barrier; BBTB, Blood-brain tumor barrier; CNS, Central nervous system; CBZ, Cabazitaxel; csGRP78, Cell surface GRP78; CT, Computed tomography; CsNPs, Chitosan-based nanoparticles; CpG, Cytosine-guanosine motifs; DAMPs, Damage-associated molecular patterns; ICAM-1, Intercellular adhesion molecule 1; IFN-γ, Interferon-gamma; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-17, Interleukin-17; JAM, Junctional adhesion molecules; MTX, Methotrexate; MS, Minoxidil sulfate; nAChRs, Nicotine acetylcholine receptors; NF-κB, Nuclear factor-κB; NTS, Nucleus tractus solitarii; O^6BTG, O^6-(4-bromothenyl) guanine; SQV, Saquinavir; PTX, Paclitaxel; Pen, Penetratin; P-gp, P-glycoprotein; siRNA, Small interfering RNA; SLN, Solid lipid nanoparticles; RME, Receptor-mediated endocytosis; VCAM, Vascular cell adhesion molecule; TNF-α, Tumor necrosis factor-alpha; VEGF, Vascular endothelial growth factor; VM, Vasculogenic mimicry; VES-g-PLL, Vitamin E succinate-grafted ε-polylysine; ZO, Zonula occludens; TAMs, Tumor-associated macrophages; BTZ, Bortezomib; DOX, Doxorubicin; BECs, Brain endothelial cells; BMTCs, Brain metastatic tumor cells; EGFR, Epidermal growth factor receptor; FRs, Folate receptors; CVOs, Certain circumventricular organs; FA, Folic acid; GLUT1, Glucose transporter-1; GBM, Glioblastoma; GFP, Green fluorescent protein; HG-NPs, High-grade NPs; HBMEC, Human brain microvascular endothelial cells; hIR, Human insulin receptor; LPs, Liposomes; LBNPs, Lipid-based nanoparticles; LDLRs, Low-density lipoprotein receptors; LRPs, LDLR-related proteins; LIFU, Low-intensity pulsed focused ultrasound; mAbs, Monoclonal antibodies; MMPs, Matrix metalloproteinases; NLC, Nanostructured lipid carriers; pDNA, Plasmid DNA; MS, Multiple Sclerosis; PEO, Poly(ethylene oxide); PEG, Polyethylene glycol; PUR, Polyurethane; PD-1, Programmed cell death protein 1; ROS, Reactive oxygen species; RMT, Receptor-mediated transcytosis; RES, Reticuloendothelial system; RT, Rivastigmine; SPIONs, Superparamagnetic iron oxide NPs; TSLs, Temperature-sensitive liposomes; TMZ, Temozolomide; TJ, Tight junction; TAT, Trans-activator of transcription; Tf, Transferrin; TBI, Traumatic Brain Injury; TPP, Tripolyphosphate.

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1. Introduction

The blood–brain barrier (BBB), a term coined by Lewandowsky and colleagues, delineates a critical frontier in our understanding of neurological function and therapeutic intervention (Lewandowsky, 1909; Lossinsky et al., 1986). Its discovery, rooted in the unyielding observations of intravenous versus intraventricular injections, heralded a paradigm shift in our comprehension of cerebral physiology. Comprised primarily of central nervous system (CNS) endothelial cells, astrocytes, and pericytes, the BBB orchestrates a symphony of cellular interactions, maintaining the delicate balance of the brain microenvironment while safeguarding against external threats. Yet, while the BBB stands as a bastion of protection for the brain, its formidable barrier presents a double-edged sword. On one hand, its integrity is paramount for neurological homeostasis and proper brain function. However, this very selectivity poses formidable challenges for diagnosing and treating a myriad of neurodegenerative diseases, which afflict millions worldwide (Keaney et al., 2015). Alzheimer's, Parkinson's, cancer, and a litany of other conditions cast a long shadow over human health, necessitating targeted therapeutic delivery to the brain (Ding et al., 2020; Hu et al., 2023; Hui et al., 2024; Xi et al., 2024; El-Gayar et al., 2020).

Traditionally, drug delivery across the BBB has been akin to navigating a labyrinth, with few options capable of circumventing its defenses. Tight junction (TJ) modulation and drug molecule modification have shown promise, yet their efficacy is often hampered by adverse effects or limited applicability (Power et al., 2022). The Trojan horse strategy, while intriguing, grapples with the BBB's discerning nature, and the omnipresent P-glycoprotein (P-gp) adds another layer of complexity, thwarting drug efflux even after successful penetration. In recent years, however, a beacon of hope has emerged on the horizon of neuropharmacology: nanotechnology (Nowak et al., 2020). With its arsenal of nanomaterial-based carriers, nanotechnology offers a promising avenue for traversing the BBB with precision and efficacy. These nanoparticles, characterized by their diminutive size, robust drug-loading capacity, and biocompatibility, herald a new era in drug delivery, circumventing the BBB without compromising its structural integrity or functionality (Saraiva et al., 2016).

As we stand at the precipice of this transformative juncture, the exponential growth of research in NP-based drug delivery across the BBB underscores not only its emergence as a burgeoning field but also its immense potential for clinical application. With each stride forward, we inch closer to unlocking the mysteries of the BBB and ushering in a new dawn of therapeutics for neurological disorders, offering renewed hope for millions worldwide. Organic NPs, in particular, have emerged as promising drug carriers due to their highly modifiable characteristics. These NPs can be engineered to possess specific properties that enhance their ability to cross the BBB, such as size, zeta potential (surface charge), high biocompatibility, low toxicity, and surface functionalization. Additionally, organic NPs can be designed to release their therapeutic payloads in a controlled manner, improving the efficacy at the target site of action and reducing the side effects of the drugs.

This review paper delves into the complex realm of administering therapeutic and diagnostic agents for brain diseases, focusing on the challenge of traversing the blood–brain barrier using organic nanoparticles. This work stands out due to its thorough and insightful examination, transcending mere summaries of recent developments to offer a profound comprehension of the challenges and opportunities present in this domain. We carefully analyze the development and application of organic nanoparticles, emphasizing their functional surface modifications, adaptable preparation techniques, mechanisms of action, drug loading and release kinetics, and therapeutic outcomes. In contrast to current reviews (Tan et al., 2022; Kulkarni et al., 2024; Wu et al., 2023; Wu et al., 2023; Zha et al., 2024; Teixeira et al., 2023; Ceña and Játiva, 2018), we highlight the crucial importance of biochemical processes and physicochemical properties—especially surface modifications—in enhancing BBB penetration. Additionally, we offer an insightful outlook on the present accomplishments and future possibilities of nanoparticle-based technologies in the treatment of neurological disorders. We carefully evaluate the clinical translation of organic nanoparticles, emphasizing both successful implementations and the fundamental causes of setbacks in moving from laboratory studies to practical therapeutic applications. Through the integration of these varied elements, our review provides innovative perspectives and actionable recommendations, establishing itself as an essential resource for the progression of therapies aimed at the brain and for connecting research with clinical application.

2. Physiology and histology of BBB

The BBB is essential for controlling the movement of chemicals into the cerebrospinal fluid. It allows certain molecules such as oxygen, carbon dioxide, and hormones to pass through while preventing pathogens, solutes, and large hydrophilic molecules from entering. Glucose and other metabolic products are transported across the barrier by specialized proteins with great efficiency. Furthermore, it serves as a protective shield that obstructs specific immunological elements from accessing the CNS, so safeguarding the brain from potential damage. The structures responsible for integrating sensory and secretory functions within neural circuits in the brain, such as the circumventricular organs and choroid plexus, possess capillaries that exhibit a high level of permeability (Kadry et al., 2020; Chen et al., 2023; Yang et al., 2023). The BBB is primarily formed by tight connections between endothelial cells of brain capillaries, which effectively limit the transport of solutes. TJs are composed of transmembrane proteins, including occludin, claudins (such as Claudin-5), and junctional adhesion molecules (JAM) such as JAM-A. Their stability is preserved by a protein complex comprising scaffolding proteins such as zonula occludens-1 (ZO-1) (Fig. 1).

The endothelial cells that form the inner lining of the brain capillaries have a vital function in preserving the integrity of the BBB (Alajangi et al., 2022). The cells are firmly interconnected via junctions, creating an unbroken barrier that blocks the entry of big chemicals and infections from the bloodstream into the brain. The BBB's ability to selectively allow certain substances to pass through depends on the strong connections between endothelial cells. Transmembrane proteins like occludins, claudins, and JAMs play a crucial role in sealing the barriers between cells and limiting the diffusion of substances. Astrocytes, specialized glial cells, are essential to BBB function (Table 1) (Wu et al., 2023).

Astrocytes' end-feet build a network of processes around blood arteries and regulate brain extracellular fluid. Astrocytes regulate BBB permeability by releasing signaling chemicals and supporting endothelial metabolism. BBB capillaries include contractile pericytes. They work with endothelial cells and astrocytes to regulate blood flow, blood vessel wall integrity, and BBB permeability. BBB endothelial cells and pericytes are supported by the basement membrane. The BBB is stabilized by extracellular matrix proteins such as collagen, laminin, and fibronectin. (Fig. 2) (Schiera et al., 2024; Song et al., 2024).

The BBB regulates material exchange between the circulation and brain extracellular fluid through multiple mechanisms. By carefully restricting chemical and cell passage, the BBB maintains CNS homeostasis. Tight connections connect brain capillary endothelial cells. These junctions block big molecules and polar chemicals from diffusing between cells (Manu et al., 2023). The BBB uses specialized transport networks to let needed nutrients, ions, and chemicals enter the brain while blocking hazardous substances. These transport systems include Endothelial cell membrane transport proteins carry glucose, amino acids, and nucleosides across the BBB. Insulin and transferrin (Tf) can penetrate the BBB via receptor-mediated endocytosis (RME) and endothelial transcytosis. Efflux transporters like P-glycoprotein (P-gp) actively remove drugs and poisons from brain endothelial cells (BECs) into the circulation, minimizing brain buildup. The BBB controls

metabolic waste exchange and preserves neuronal function. It regulates ion, water, and metabolic byproduct inflow and efflux to sustain neuronal activity and remove brain poisons. Neurovascular coupling coordinates cerebral blood flow and neuronal activity via the BBB. By adjusting blood flow to neuronal demand, it supplies active brain areas with oxygen and nutrients (Niazi, 2023). Astrocytes are essential to BBB permeability and function. They release signaling chemicals that influence TJ protein expression and endothelial cell function. Astrocyte endfeet protect blood vessels and strengthen the BBB. By blocking the circulation immune cells and chemicals, the BBB gives the CNS immunological privilege. The CNS maintains immunological homeostasis through specialized mechanisms like the brain's lack of lymphatic outflow and immune-regulatory chemicals (Verkhratsky and Pivoriūnas, 2023; Shen et al., 2021). The BBB serves as a robust shield, safeguarding the delicate brain tissue from any potential threats posed by pathogens and harmful substances. Infections rarely make their way to the brain through the bloodstream, thanks to the remarkable effectiveness of this barrier. Coping with brain infections can provide a substantial obstacle because of the complexity in transporting big antibodies across the BBB. Only specific antibiotics has the capability to traverse this barrier. At times, it may be necessary to administer medication directly into the cerebrospinal fluid in order to access the brain, bypassing the BBB via the blood-cerebrospinal fluid barrier (Patabendige and Janigro, 2023).

2.1. Specialized permeable zones

Certain circumventricular organs (CVOs) feature specialized hybrid capillaries that exhibit lower permeability compared to typical brain capillaries but are more porous than the boundary zones between brain tissue protected by BBB and areas exposed to blood signals. Notably, both the median eminence (part of the hypothalamic arcuate nucleus) and the region postrema border (nucleus tractus solitarii, or NTS) contain such zones (Verheggen et al., 2020). These areas serve as rapid transit zones within the NTS and arcuate nucleus, distinct brain structures involved in different neural circuits. They function to swiftly receive blood impulses and convert them into neural output. The hypothalamic arcuate nucleus and the median eminence share a permeable capillary zone, which is enhanced by wide pericapillary spaces. This allows solutes to flow in both directions, suggesting that the median eminence is a sensory organ in addition to a secretory organ. Plans for regulating and bridging the BBB (Song and Choi, 2023; Fakouri et al., 2024; Zhu et al., 2024; Hatami et al., 2023).

Severe conditions that impact the CNS include brain tumors, cerebrovascular diseases, and neurodegenerative disorders like multiple sclerosis, Alzheimer's disease, and Parkinson's disease. Unfortunately, there aren't many effective ways to get medications past the brain's inherent protective barriers that keep homeostasis and stop them from entering the CNS (Kesidou et al., 2023; Hatami et al., 2023). This means that treatments for these difficult conditions are limited. Invasive methods for illness management and symptom control frequently provide a range of medications. Brain drug delivery has progressed to include other intrusive techniques such as deep-brain stimulation, intracranial implantation, and convection-enhanced delivery (Partridge et al., 2022; Farokhi et al., 2024).

2.2. Passive and active transcytosis

Two potential pathways exist across the microvascular endothelial layer for passive transcytosis, aka non-specific transfers: transcellular and paracellular (Table 2).

The tight connections between cell gaps, which limit the movement of ions, polar solutes, and larger molecules, prevent the paracellular pathway. Although TJs have their flaws, small soluble molecules can still pass through this pathway. Brain illnesses often affect the integrity of BBB (Khalil et al., 2024). One therapy strategy involves reducing the expression of tight junction proteins to utilize the paracellular route. For instance, minoxidil sulfate (MS) acts as a modulator by inhibiting TJ proteins, particularly affecting potassium channel anchoring. Zhou et al. developed CTX-mHph2-III-62 % ligand-modified NPs to target brain tumors, incorporating minoxidil, lexiscan, and NECA as modulators. The permeability of terpolymer III-62 % NPs across the BBB is limited without additional modifications. Co-encapsulating these NPs could enable the targeted release of BBB modulators at tumor sites, enhancing their ability to penetrate the BBB via the paracellular pathway. Han et al. designed NPs loaded with minoxidil using hyaluronic acid to target brain metastatic cancers. Hyaluronic acid can specifically target the CD44 cell surface receptor, which is overexpressed in breast cancer (Miao et al., 2019; Mahmoudvand et al., 2023; Zhao et al., 2024). In

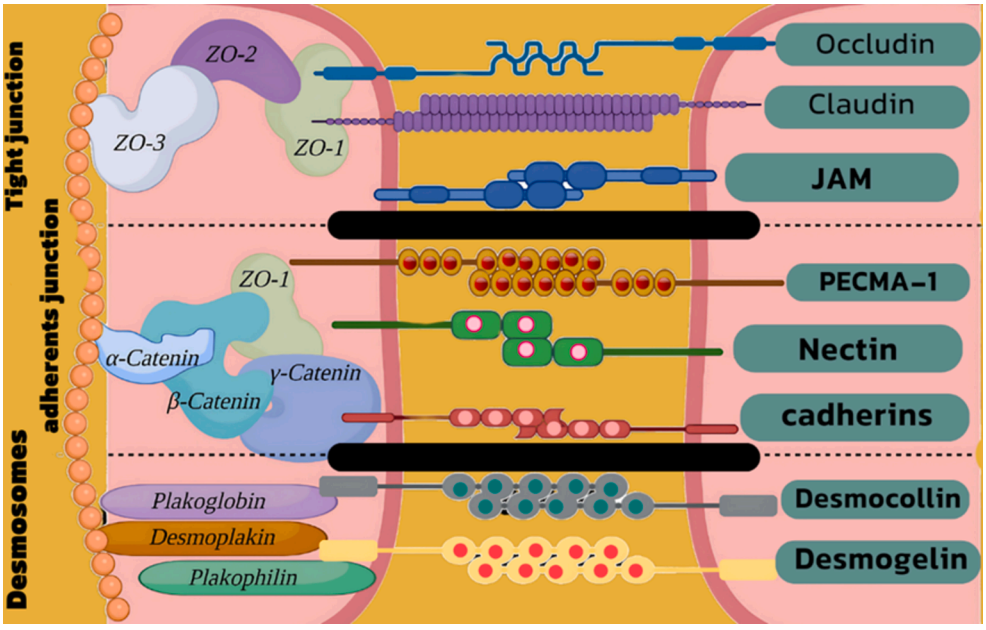


Fig. 1. A visual representation highlighting the crucial role of tight junctions, adherent junctions, and desmosome proteins in maintaining the selective permeability of the BBB, crucial for brain homeostasis and protection..

models of breast cancer brain metastases, these NPs (M@H-NPs) successfully crossed the BBTB, entered BMTCs, and effectively treated the cancer by inhibiting drug efflux from BMTCs, thanks to the CD44 targeting and MS enhancement (Horowitz et al., 2023).

Carriers should enter and carry therapeutic substances via the transcellular pathway rather than the paracellular pathway. In a nutshell, chemicals can undergo carrier-mediated or receptor-mediated transcytosis to enter cell membranes in a top-down or bottom-up fashion. For instance, the transcellular pathway is primarily responsible for the transport of lipophilic carriers as well as cationic amino acids and a few other recognized carrier systems (Pawar et al., 2022).

Except for hydrophilic chemicals with a mass below 150 Da and very hydrophobic compounds with a mass lower than 400–600 Da, most medications cannot enter the brain via passive transcytosis due to the tightness of BBB. Therefore, if the administration of medications with a greater molecular weight requires passive transcytosis, then methods to temporarily disrupt the BBB or increase its permeability will be sought after (Wu et al., 2023).

2.3. Approaches of BBB disruption due to disease

The BBB plays a crucial role in maintaining the balance of the brain by tightly controlling the movement of different substances between the bloodstream and CNS. The basement membrane is an essential component of the BBB, a highly selective semipermeable membrane that separates the circulating blood from the brain extracellular fluid in the CNS. The BBB is crucial for maintaining brain homeostasis and protecting the brain from harmful substances (Daneman and Prat, 2015; Hao et al., 2023).

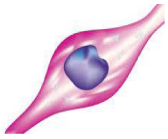
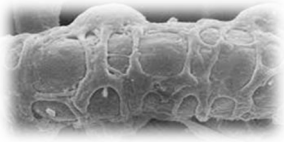
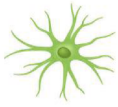
Degradation of the basement membrane in the context of the BBB can occur due to various factors, including inflammation, injury, or disease processes. For example, in conditions like multiple sclerosis, Alzheimer's disease, or stroke, the integrity of the BBB can be compromised, leading to increased permeability and breakdown of the basement membrane (Archie et al., 2021; Molaei et al., 2022; Zhang et al., 2021).

Inflammation plays a significant role in the degradation of the basement membrane associated with BBB dysfunction. Inflammatory mediators can disrupt the TJs between endothelial cells and lead to increased permeability. Additionally, enzymes released during inflammation, such as matrix metalloproteinases (MMPs), can directly degrade the basement membrane components, further compromising BBB integrity. Understanding the mechanisms underlying basement membrane degradation in the context of BBB dysfunction is crucial for developing treatments aimed at preserving or restoring BBB function in various neurological disorders (Fig. 3) (Yang et al., 2022; Varatharaj and Galea, 2017).

Its integrity and function can be compromised by various brain diseases, each with its own set of mechanisms, often involving inflammation, oxidative stress, and alterations in TJ proteins (Table 3) (Fig. 4) (Archie et al., 2021; Deng et al., 2024). Here's an overview of how different brain diseases can influence the BBB, alongside the physiological and chemical changes associated with each:

Parkinson's disease: Parkinson's disease is associated with disruption of the BBB, which can be attributed to a variety of linked variables. An important process includes oxidative stress, which occurs when there is an imbalance between reactive oxygen species (ROS) and antioxidants. Endothelial cells of the BBB can be susceptible to damage caused by oxidative stress, which can result in heightened permeability. In addition, inflammation plays a crucial role, as activated microglia and infiltrating immune cells release pro-inflammatory cytokines and chemokines (Chung et al., 2022). These inflammatory mediators have the potential to disrupt TJ proteins, which can compromise the integrity of the BBB. In addition, the accumulation of alpha-synuclein, a protein commonly found in Parkinson's disease, has been linked to dysfunction in the BBB. Aggregates of alpha-synuclein have the ability to trigger neuroinflammation and have a direct impact on the permeability of the BBB (Lau et al., 2023). Multiple physiological and chemical alterations take place when the BBB is compromised in Parkinson's disease. Increased concentrations of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are observed in the brain tissue, causing the disruption of the BBB. These cytokines facilitate the activation of MMPs, leading to the degradation of extracellular matrix proteins and the disruption of tight junctions (Gopinath et al., 2023; Zhuo et al., 2024). In addition, oxidative stress can result in the generation of ROS, which has the potential to harm endothelial cells and undermine the integrity of the BBB. The increased permeability of the BBB in Parkinson's disease is influenced by alterations in the production and activity of TJ proteins,

Table 1
BBB's cells and their functions of them.

Aspect	 Endothelial Cells	 Pericytes	Astrocytes 	References
Structure	Line the inside of brain capillaries.	Found near capillaries, within their walls.	Wrap around blood vessels with star-like shapes	(Wu et al., 2023; Kadry et al., 2020; Lochhead et al., 2020; Galea, 2021; Kazempour and Balogh, 2024)
Morphology	Flat cells with tight connections	Small, spindle-shaped with long extensions	Star-shaped with many branches	(Chen et al., 2024; Manu et al., 2023; Armulik et al., 2010)
TJs	Create a seal to prevent leaks between cells.	Help keep the barrier strong.	Send signals to support barrier function.	(Luissint et al., 2012; Zheng et al., 2023; Sugiyama et al., 2023)
Transporters	Allow nutrients in and remove waste.	Control blood flow and new blood vessel growth.	Provide nutrients and protect the barrier.	(Johnsen et al., 2017; Nilles et al., 2022; Hall et al., 2014)
Barrier Function	Keep harmful substances out of the brain.	Support barrier stability and blood flow.	Help control barrier leaks and support neurons.	(Abbott, 2002; Daneman et al., 2010; Lippmann et al., 2012; Jafarabady et al., 2024)
Neuroprotection	Block toxins, germs, and immune cells from entering.	Protect the barrier and brain.	Release substances that reduce inflammation.	(Guo et al., 2008; Yuan et al., 2023; Brown et al., 2019; Khaniki et al., 2023)
Dysfunction	Gaps form, causing inflammation and brain damage.	Detachment weakens the barrier, causing leaks.	Dysfunction leads to inflammation and barrier breakdown.	(Galea, 2021; Fang et al., 2023; Preininger and Kaufer, 2022; Yuan et al., 2023)
Histopathology	Swelling and leaks allow harmful cells into the brain.	Loss of connection causes barrier failure.	Overactivity or dysfunction weakens the barrier.	(Galea, 2021; Dallasta et al., 1999; Krueger et al., 2019; Price et al., 2016)

including occludin, claudins, and ZO (Hu et al., 2022; Hao et al., 2023).

Multiple Sclerosis (MS): Multiple Sclerosis (MS) is an inflammatory condition that involves inflammation, the loss of myelin, and the degradation of nerve cells in the CNS. BBB plays a crucial role in MS pathology, as its dysfunction allows immune cells to infiltrate the CNS and contribute to tissue damage. In MS, autoreactive immune cells, primarily T cells, are activated in the periphery and migrate across the BBB into the CNS. These immune cells recognize myelin components as antigens, initiating an inflammatory cascade within the CNS (Papiri et al., 2023). Upon entering the CNS, immune cells that have been activated release pro-inflammatory cytokines, including interferon-gamma (IFN-γ) and interleukin-17 (IL-17). These cytokines stimulate the production of adhesion molecules on the endothelial cells of the BBB, making it easier for more immune cells to enter the CNS. Inflammatory mediators released by immune cells can disrupt the integrity of TJs between endothelial cells of the BBB. This disruption leads to increased permeability, allowing immune cells and potentially harmful molecules to penetrate into the CNS parenchyma. In MS, there is an upregulation of MMPs within the CNS (Zhang et al., 2022; Meyer-Arndt et al., 2023). MMPs degrade extracellular matrix proteins and TJ proteins, further compromising BBB integrity and facilitating immune cell infiltration into the CNS. MS patients exhibit increased concentrations of pro-inflammatory cytokines, including IFN-γ, IL-17, and TNF-α, in the CNS (Galea, 2021). These cytokines facilitate the breakdown of the BBB by stimulating the production of adhesion molecules and promoting the breaking of TJs. In addition, there is a noticeable increase in the production and activity of MMPs, including MMP-2 and MMP-9, in MS lesions (Yang et al., 2019; Otaghvar et al., 2022). MMPs break down proteins in the extracellular matrix and TJs proteins, causing disruption of the BBB and an increase in permeability. Chemokines, such as CCL2 (also known as MCP-1) and CXCL12 (also known as SDF-1), are upregulated in MS lesions. These chemokines play a role in immune cell recruitment across the BBB and into the CNS, exacerbating inflammation and tissue damage. In addition, Oxidative stress is heightened in MS, leading to the production of ROS within the CNS. ROS can directly damage endothelial cells of the BBB, contributing to BBB dysfunction and increased permeability (Balasa et al., 2021).

Stroke: Stroke, whether it is caused by a lack of blood flow (ischemic) or bleeding (hemorrhagic), causes damage to the BBB. This damage allows blood components and inflammatory cells to leak into the brain tissue (Okada et al., 2020).

Ischemic Stroke: Decreased blood flow during ischemic stroke leads to a lack of oxygen and a depletion of energy in the affected area of the brain. Hypoxia can lead to the generation of ROS in the brain, causing oxidative stress. Ischemia triggers the release of pro-inflammatory cytokines, such as TNF-α and IL-1β. These cytokines are released by activated microglia and infiltrating immune cells. Inflammatory molecules and reactive oxygen species can harm the connections between cells in the BBB, leading to an increase in its permeability (Qin et al., 2022; Salaudeen et al., 2024).

Hemorrhagic Stroke: In hemorrhagic stroke, blood leaks into the brain parenchyma, directly disrupting the BBB. The presence of blood components in the brain triggers an inflammatory response, leading to the activation of microglia and the recruitment of immune cells. Hemoglobin breakdown products and inflammatory mediators activate MMPs, which degrade extracellular matrix proteins and TJ proteins of the BBB. Following a stroke, the brain shows increased levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines cause the breakdown of the BBB by stimulating the production of adhesion molecules and facilitating the breaking of TJs (Mayer and Fischer, 2024; Cheng et al., 2024). MMPs, specifically MMP-2 and MMP-9, are increased in expression in the brain following a stroke. MMPs break down proteins in the extracellular matrix and TJs, resulting in the disruption of the BBB and an increase in permeability. Oxidative stress occurs in both ischemic and hemorrhagic strokes, leading to the production of ROS within the brain. ROS can directly damage endothelial cells of the BBB, contributing to BBB dysfunction and increased permeability. Inflammatory mediators, such as prostaglandins and leukotrienes, are released during the inflammatory response following stroke. These mediators can induce vasodilation, increase vascular permeability, and promote leukocyte infiltration across the BBB (Wang et al., 2024; Duan et al., 2024).

Brain Tumors: Brain tumors have a profound impact on the BBB, altering its structure and function in several ways. This disruption contributes to increased permeability and facilitates the progression of the tumor within the brain. Brain tumors, particularly gliomas, release angiogenic factors such as vascular endothelial growth factor (VEGF). These factors stimulate the growth of new blood vessels (angiogenesis) within and around the tumor (Mo et al., 2021; Piranfar et al., 2024). However, these newly formed blood vessels are often abnormal and leaky, compromising the integrity of the BBB. Tumor cells secrete MMPs, enzymes that degrade the extracellular matrix surrounding blood vessels. MMPs break down components of the BBB, including TJ proteins and basement membrane proteins. This degradation increases BBB permeability, allowing tumor cells to infiltrate surrounding brain tissue. As brain tumors grow, they can exert physical pressure on nearby blood

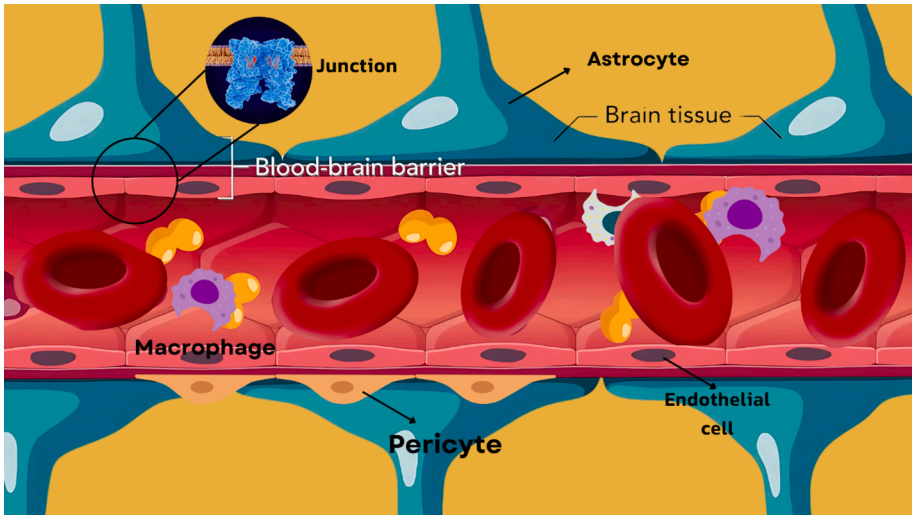


Fig. 2. Unraveling the Guardians of the Blood-Brain Barrier: A Complex Interplay Among Endothelial Cells, Pericytes, Astrocytes, and Microglia in Preserving BBB Integrity.

Table 2
Passive and active transcytosis for brain targeting, including pathways, methods, carriers, and key findings.

Pathway	Method and Carrier	Key Findings	References
Paracellular Pathway	Modulation of TJ proteins (e.g., minoxidil sulfate (MS))	• MS decreases TJ protein activity, increasing paracellular transport. • Ligand-modified NPs containing MS, lexiscan, and NECA enhance BBB permeability, facilitating drug delivery to brain tumor sites. • NPs loaded with minoxidil and hyaluronic acid target brain metastatic cancers by enhancing paracellular transport and exploiting CD44 receptor. • Effective treatment of breast cancer brain metastases models achieved through NPs' penetration of BBT) and internalization into brain metastatic tumor cells (BMTCs).	(Luissint et al., 2012; Pulgar, 2019; Gu et al., 2013; Miao et al., 2019; Wu et al., 2023)
	Disruption of TJs (e.g., ultrasound, hyperosmotic agents)	• Ultrasound and hyperosmotic agents temporarily disrupt tight junctions, increasing paracellular transport across the BBB. • This method allows for enhanced delivery of therapeutics, including chemotherapeutic agents and NPs, to brain tumors and other neurological disorders. • Ultrasound-mediated BBB disruption shows promise as a non-invasive and reversible method for enhancing drug delivery to the brain.	(Kovacs et al., 2017; Gandhi et al., 2022; Librizzi et al., 2022; Burks et al., 2021; Linville et al., 2020)
Transcellular Pathway	Carrier-mediated or receptor-mediated transcytosis (RMT)	• Lipid NPs can enter brain lesions via transcellular pathways, demonstrating self-diffusion at the lesion site. • OX26-PEG-CSLN NPs loaded with baicalin exhibit improved BBB crossing and extended effective duration of drugs. • Most medications cannot passively cross the BBB, except for hydrophilic chemicals below 150 Da and very hydrophobic compounds below 400–600 Da. • Methods to temporarily disrupt the BBB or increase its permeability are sought for the administration of medications with greater molecular weight.	(Pardridge, 2012; Stamp et al., 2023; Cornelissen et al., 2023; Liu et al., 2015; Wong et al., 2013)
	Ligand Conjugation	• Ligand-conjugated systems offer targeted delivery to brain cells and tissues via RMT. • Tf, insulin, and folate receptors are commonly targeted for brain drug delivery using ligand conjugation. • Ligand-modified NPs demonstrate enhanced BBB penetration, improved target specificity, and increased therapeutic efficacy in preclinical models of brain tumors, neurodegenerative diseases, and other neurological disorders. • Ligand conjugation provides a versatile approach for enhancing drug delivery to the brain across various neurological conditions.	(Moreira et al., 2024; Gao et al., 2024; Alibolandi et al., 2018; Choudhury et al., 2018; Anthony et al., 2021; Sharma et al., 2019; Rajwar et al., 2023; Bolhassani et al., 2021)

vessels and surrounding brain tissue. This physical compression can lead to mechanical disruption of the BBB, compromising its ability to regulate the passage of substances into the brain (Wang et al., 2021; Soltani et al., 2021). The disruption of the BBB by brain tumors results in increased vascular permeability. This enhanced permeability facilitates the escape of chemicals carried by the blood, inflammatory cells, and even tumor cells into the brain tissue. Brain tumors induce an inflammatory reaction in the surrounding microenvironment. Microglia and infiltrating leukocytes, which are immune cells, secrete pro-inflammatory cytokines and chemokines. The inflammatory mediators facilitate the breakdown of the BBB by inducing the production of adhesion molecule genes on endothelial cells and by breaking TJ proteins. The altered BBB in brain tumors can hinder the delivery of chemotherapeutic agents to the tumor site. This reduced drug delivery contributes to chemoresistance and limits the efficacy of systemic treatments (Han and Jiang, 2021; McDonald et al., 2023; Souri et al., 2024; Souri et al., 2024; Shahvandi et al., 2023).

Traumatic Brain Injury (TBI): Traumatic Brain Injury (TBI) can lead to significant alterations in the BBB, resulting in increased permeability and potential neurotoxicity. TBI causes immediate mechanical damage to the BBB, disrupting the structural integrity of blood vessels and endothelial cells. This disruption leads to increased permeability and allows blood components and potentially harmful substances to enter the brain parenchyma. Following the initial trauma, secondary injury processes occur, including neuroinflammation, excitotoxicity, and oxidative stress. These processes exacerbate BBB dysfunction and contribute to further damage (Sivandzade et al., 2020; Huang et al., 2022; Razavi et al., 2024). TBI initiates an inflammatory cascade within the brain, marked by the activation of microglia and the recruitment of peripheral immune cells. This inflammatory response involves the release of cytokines and chemokines, which play a pivotal role in compromising the integrity of the BBB through the upregulation of adhesion molecules and the destabilization of TJ proteins. Excessive glutamate release caused by TBI exceeds normal levels, leading to the activation of glutamate receptors and the subsequent entry of calcium into neurons, ultimately resulting in the death of these cells. This excitotoxic process not only contributes to oxidative stress but also exacerbates BBB disruption (Zhao et al., 2023; Postolache et al., 2020; Feng et al., 2023). Furthermore, TBI is associated with heightened levels of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 in the brain, which further promote BBB breakdown by enhancing adhesion molecule expression and disrupting TJs. The injury-induced surge in ROS directly impacts BBB endothelial cells, exacerbating BBB dysfunction and permeability. Additionally, TBI triggers the upregulation of MMPs, particularly MMP-2 and MMP-9, which degrade BBB extracellular matrix and TJ proteins, contributing to increased BBB permeability. Disruption of ion homeostasis by TBI further compounds cellular dysfunction and augments BBB permeability. Changes in ion concentrations, particularly calcium, contribute to neuronal damage and exacerbate BBB dysfunction (Yang et al., 2022; Rana and Musto, 2018).

Infections: Infections can impact the CNS, leading to notable alterations in the BBB. This can result in heightened permeability, enabling pathogens and inflammatory mediators to enter the brain tissue. Pathogens, such as bacteria, viruses, fungi, and parasites, can directly invade the CNS by breaching the BBB through various mechanisms, including adhering to and disrupting endothelial cells or exploiting transcellular or paracellular routes (Archibald and Quisling, 2013; Drummond, 2023; Liu et al., 2024). In response to infection, the immune system triggers

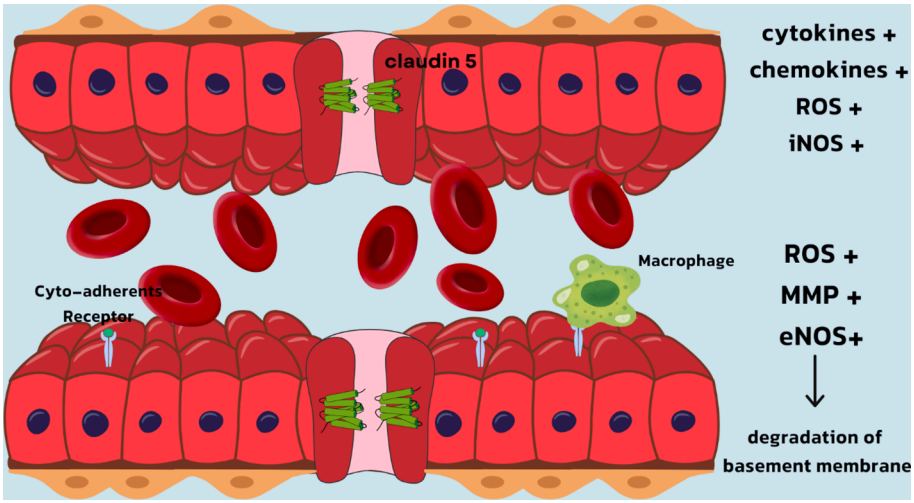


Fig. 3. The degradation of the basement membrane compromises BBB integrity, increasing permeability and contributing to neuroinflammation and neuronal damage. This highlights the basement membrane's crucial role in maintaining BBB function and brain homeostasis. BBB: Blood-Brain Barrier, ROS: Reactive Oxygen Species, iNOS: Inducible Nitric Oxide Synthase, MMP: Matrix Metalloproteinases, eNOS: Endothelial Nitric Oxide Synthase.

Table 3
Brain Disease and Physio-Chemical Changes in BBB.

Brain Disease	Physio-Chemical Changes in BBB	Drug Delivery Approaches	Causes of Disease	References
Parkinson's Disease	BBB dysfunction due to neuroinflammation; Altered TJs; Oxidative stress	NP-based drug delivery; Intranasal delivery for direct brain targeting	Dopamine neuron degeneration in the substantia nigra is linked to misfolded protein aggregates and mitochondrial dysfunction.	(Araújo et al., 2022; Tansey et al., 2022; Monge-Fuentes et al., 2021; Baskin et al., 2021; Feng et al., 2023)
Traumatic Brain Injury	BBB disruption due to mechanical trauma; Increased permeability; Inflammatory response	Intravenous administration of therapeutic agents; Intranasal delivery for direct brain access	Brain trauma from accidents or injuries causes tissue damage, inflammation, and neurological deficits.	(Cash and Theus, 2020; Inyang et al., 2020; Pandya et al., 2024; Kheirandish et al., 2022)
Epilepsy	BBB leakage due to seizures; Altered expression of transporters; Neuroinflammation	Intracerebral drug infusion; NP-based drug carriers	Abnormal brain electrical activity causes recurrent seizures, often due to genetic or structural factors.	(Marchi et al., 2012; Rempe et al., 2018; Cook et al., 2020; Bennewitz and Saltzman, 2009; Barcia and Gallego, 2009; Pracucci et al., 2021)
Alzheimer's Disease	BBB dysfunction due to beta-amyloid accumulation; Neuroinflammation; Altered transporter function	RMT for therapeutic antibody delivery; NPs for targeted drug delivery	Beta-amyloid plaques and tau tangles cause neurodegeneration, cognitive decline, and dementia.	(Wang et al., 2021; Alkhalifa et al., 2023; Sousa et al., 2023; Roghani et al., 2024; Khan et al., 2021; Wang et al., 2022; Luo et al., 2019)
Multiple Sclerosis	BBB breakdown by immune cell infiltration; Increased permeability; Inflammatory cytokine release	Liposome-based drug carriers; Monoclonal antibodies targeting immune cells	Autoimmune attacks on myelin cause demyelination, inflammation, and neurological symptoms.	(Larochelle et al., 2011; Amoriello et al., 2024; Zierfuss et al., 2024; Greco and Sarpietro, 2024; Fontoura, 2010; Nawar et al., 2022)
Brain Tumors	BBB disruption due to tumor-secreted factors; Angiogenesis; Increased permeability	Convection-enhanced delivery for direct drug administration; Polymer-based drug carriers	Abnormal cell proliferation forms brain tumors, disrupting function and inducing neuroinflammation.	(Kim et al., 2021; Mo et al., 2021; Tiwary et al., 2018; Guarnaccia et al., 2018; D'Amico et al., 2021; Caraway et al., 2022; Souri et al., 2024; Mousavi et al., 2024)
Ischemic Stroke	Increased BBB permeability; TJ disruption; Inflammatory response	Liposomal drug delivery; Focused ultrasound for localized drug delivery	Blocked cerebral vessels reduce oxygen, causing neuronal damage.	(Sugiyama et al., 2023; Mathias et al., 2024; Bernardo-Castro et al., 2020; Zhang et al., 2024; Guo et al., 2022; Feng and Li, 2024)

inflammatory pathways in the CNS, resulting in the production of pro-inflammatory cytokines, chemokines, and other inflammatory substances. These substances contribute to the breakdown of the BBB by causing the production of adhesion molecules, which are found on endothelial cells, and disrupting TJ proteins (Millán Solano et al., 2023; Ramesh et al., 2013; Li et al., 2022). Some pathogens release neurotoxins or toxins that can directly damage endothelial cells of the BBB, further increasing permeability and disrupting BBB integrity. Infections can also indirectly affect the BBB by triggering secondary processes such as excitotoxicity, oxidative stress, and activation of MMPs, which further compromise BBB function and integrity. Increased concentrations of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, are detected in the CNS after infection (Rajeev et al., 2022; Song et al., 2020). These cytokines have a role in the breakdown of the BBB by stimulating the production of adhesion molecules and breaking TJs. Infections cause an elevation in the formation of ROS in the CNS. This can directly harm the endothelial cells of the BBB, resulting in malfunction and heightened permeability of the BBB. MMPs, specifically MMP-2 and MMP-9, are elevated in expression during CNS infections (Yarlagadda et al., 2009). They break down proteins in the extracellular matrix and TJ proteins of the BBB, resulting in the rupture of the BBB and an increase in its permeability. Increased concentrations of chemokines, including CCL2 and CXCL12, are detected in the CNS during infection. These chemokines contribute to the recruitment of immune cells from the BBB into the CNS, intensifying inflammation and causing the collapse of the BBB (Forouzandeh et al., 2022; Wang et al., 2023).

Epilepsy: Epilepsy, a condition characterized by recurrent seizures, can impact the BBB in several ways, resulting in alterations to the

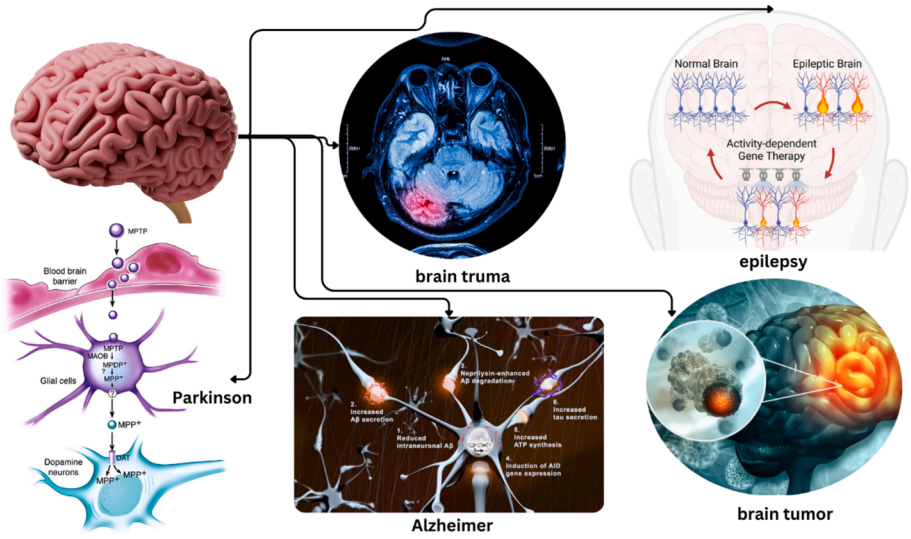


Fig. 4. BBB dysfunction contributes to neurological conditions such as Alzheimer's disease, multiple sclerosis, stroke, and traumatic brain injury by allowing harmful substances and immune cells into the brain, leading to neuroinflammation and neuronal damage. Addressing BBB dysfunction is key to developing targeted therapies.

structure and function of the barrier. Seizures can induce brain inflammation by triggering the activation of microglia and astrocytes, which then release pro-inflammatory chemicals such as IL-1β, TNF-α, and IL-6. These chemicals have the ability to harm the BBB by causing an increase in the expression of adhesion molecules and affecting the integrity of TJs (Sumadewi et al., 2023; Bronisz et al., 2023). Additionally, seizures can cause excessive neuronal activity and glutamate release, leading to excitotoxicity and calcium influx, which can damage neurons and cause oxidative stress, impacting the BBB. Seizures can also affect cerebral blood flow, leading to changes in BBB permeability and potentially allowing inflammatory mediators and other substances to enter the brain (Green et al., 2021). Recurrent seizures can cause neuronal injury and death, releasing damage-associated molecular patterns (DAMPs) and inflammatory signals that can worsen neuroinflammation and BBB dysfunction. High levels of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6 are found in the brain during seizures, contributing to BBB breakdown by promoting adhesion molecule expression and TJ disruption (Foiadelli et al., 2023). Seizures result in increased production of ROS within the brain. ROS can directly damage endothelial cells of the BBB, contributing to BBB dysfunction and increased permeability. Excessive glutamate release during seizures leads to excitotoxicity, causing neuronal damage and oxidative stress. Glutamate excitotoxicity contributes to BBB disruption and increased permeability. Seizures induce the release of various inflammatory mediators, including prostaglandins and leukotrienes. These inflammatory mediators contribute to BBB breakdown by promoting vascular permeability and leukocyte infiltration into the brain parenchyma. Understanding these disease-specific impacts on the BBB, along with associated physiological and chemical changes, is crucial for developing targeted therapeutic strategies aimed at preserving BBB function and mitigating the progression of brain diseases (Olowe et al., 2020; Madireddy and Madireddy, 2023).

3. Organic nanoparticles

3.1. Lipid–based nanoparticles

Important components of lipid-based NPs (LBNPs) include liposomes (LPs), solid lipid NPs (SLN), and nanostructured lipid carriers (NLC). These NPs have found widespread use in the creation of colloidal and precise nanoparticles (Mungroo et al., 2022). LBNPs provide various advantages similar to numerous other nanoparticles, including stability in thermal and temporal aspects, easy of preparation, significant drug-loading capabilities for specific formulations, and economical manufacturing. However, these benefits can differ based on the particular formulation and intended use (Waheed et al., 2024; Tenchov et al., 2021; Zhang et al., 2022; Waheed et al., 2022). The capacity of LBNPs to transport hydrophobic and hydrophilic molecules, together with no or very low cytotoxicity, regulated release, and longer half-life, are further benefits. In addition, chemical modifications to LBNPs may enhance drug solubility, evade immune system detection, and enable them to bind to particular receptors via antibody association (García-Pinel et al., 2019). In their lipid-based primary structure, LBNPs encapsulate and transport therapeutic substances such as drugs or nucleic acids, making them an adaptive drug delivery device. Phospholipids' amphiphilic properties make LBNPs versatile drug transporters that can bind to both hydrophobic and hydrophilic compounds, increasing their stability and solubility (Gupta et al., 2023; Razavi et al., 2024; Razavi et al., 2024; Razavi et al., 2024). Table 4 includes a comprehensive summary of various synthesis methods for LBNPs.

Crossing the BBB: Engineering LBNPs to increase their penetration into the BBB/BBTB has made tremendous progress in recent studies. To begin with, the capability of LBNPs to traverse the BBB and evade reticuloendothelial system (RET) clearance is strongly influenced by their dimensional characteristics. Research has shown that LBNPs ranging from 120 to 200 nm in particle size are more likely to cross the BBB because they are able to evade RES clearance and remain in the circulation for longer (Satapathy et al., 2021). Secondly, LBNPs that have been PEGylated are better able to evade RES and phagocytosis, have a longer half-life in circulation, and interact more easily with the BBB (Gastaldi et al., 2014; Fang et al., 2015). It has also been shown that certain receptors expressed on neurons and BECs, including apolipoprotein-E (ApoE), can be efficiently targeted by ligand functionalization on the surfaces of LBNPs. By modifying SLNs with ApoE, Neves et al. demonstrated that these NPs could traverse a BBB model, maintaining their structural integrity (Neves et al., 2017). Meanwhile, compared to the non-functionalized SLNs, ApoE-modified SLNs exhibited a higher rate of cellular internalization in their investigation. Wu et al. produced a liposome that included cabazitaxel (CBZ) nanocrystals. The liposome was modified with a D-peptide ligand called VAP and a composite ligand called pHA. This modified liposome was referred to as pV-Lip/cNC. VAP interacts with the 78-kDa glucose-regulated protein (GRP78) which is highly expressed on BBTB, vasculogenic mimicry (VM), and glioma cells. The in-vitro studies confirmed that pV-Lip/cNC could effectively target gliomas, cross barriers, and penetrate tumor spheroid (Wu et al., 2022). Therapeutic administration of pV-Lip/cNC into a mouse orthotopic glioblastoma (GBM) model greatly elevated

CBZ concentration within gliomas, leading to increased anti-glioma efficacy and an average survival time extension of 53 days. On the other hand, average survival times of 42 and 45 days, respectively, were associated with cNC-containing liposomes that were supplemented individually with VAP or pHA. Based on these results, pV-Lip/cNC can be able to cross the BBB and the BBTB to eliminate glioma cells, making it a possible candidate for effective treatment of GBM.

3.1.1. Liposomes

Liposomes are colloidal particles that self-assemble using phospholipids. These NPs consist of one bilayer of phospholipids or more. Natural or synthesized phospholipids make up liposomes, which are tiny vesicles measuring nanometers to a few micrometers in size (Torchilin, 2012). Phosphatidylethanolamine, phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, and phosphatidylinositol are all examples of phospholipids that occur naturally.

Research has shown that liposomes can encapsulate a wide variety of active drug ingredients, depending on their size, composition, charge, and efficiency (Allen and Cullis, 2013; Souri et al., 2024). The main problems with liposomes are drug leakage and scaling up (Sercombe et al., 2015). Based on lipid based nanoparticles' application for drug delivery, five distinct types have been developed to enhance specific therapeutic outcomes: pH-sensitive (Chu and Szoka, 1994; Rustad et al., 2022), long-circulating (Gabizon et al., 1997; Allen et al., 1995), cationic (Liu et al., 2020; Shim et al., 2013), conventional, and immunoliposomes (Sullivan et al., 1986; Merino et al., 2018). Modified liposomes are called niosomes (Sriraman and Torchilin, 2014; Sercombe et al., 2015; Gharbavi et al., 2018; Bartelds et al., 2018).

There are several benefits in drug delivery to using liposomes, which are closed spherical bilayer vesicles: Highly adaptable when it comes to drug loading; Liposomes typically contain a hydrophilic core in the center and a lipid bilayer around it, although they may have a single lipid bilayer (Unilamellar) or multiple lipid bilayers (Multilamellar) depending on the situation (Kumar et al., 2019). These NPs are mostly composed of glycerophospholipids, shingophospholipids, and sterols. hydrophobic drug are contained within the lipophilic core of lipid bilayers, whereas hydrophilic drugs might be located in the aqueous core or at the interface between the lipid bilayer and the surrounding aqueous phase (Fig. 5A). Liposomes have the ability to transport both hydrophobic and hydrophilic drugs, while simultaneously providing protection from dilution by bodily fluids and destruction by enzymes (Rideau et al., 2018). Liposomes also have increased bioavailability and good biocompatibility. Phospholipids are components of cell membranes that, when injected into a body with a compromised immune system, do not cause toxicity (Agrawal et al., 2017).

Both passive and active targeting are available to them for cargo delivery throughout the BBB. These carriers get an extra advantage in drug delivery across the BBB when their surfaces are functionalized with certain ligands or monoclonal antibodies (mAbs) (Kaur et al., 2004; Huwyler et al., 1996). Trans-activator of transcription (TAT), a cell-penetrating peptide, and Tf were used to achieve dual-targeted liposomal administration in a trial that treated brain glioma. Tf is a glycoprotein that responsible for transporting ferric ions (Fe^{3+}) into cells. The Tf/TAT-LP nanocomplex was able to access brain cancer cells via penetrating the endothelial cells. When compared to bare LPs, in vivo imaging revealed that the nanocomplex had a greater tumor distribution (Chen et al., 2016). Similarly, another research compared sertraline-loaded PEGylated and glycosylated LPs to determine which system would be the better drug transporter. Compared to PEGylated LPs, glycosylated LPs had a better affinity for targeting cancer cells because

Table 4
Diverse Methods for Synthesis of LBNPs.

Method	Description	Advantages	Disadvantages	References
Thin Film Hydration	Lipids are dissolved, evaporated into a thin film, hydrated to form multilamellar vesicles, and homogenized into unilamellar vesicles.	• Simple and straightforward process • Capable of encapsulating both hydrophilic and lipophilic drugs • Produces biocompatible liposomes for drug delivery	• Results in batch-to-batch variability in particle size and encapsulation efficiency • Challenging to scale up for industrial production • Sensitive to mechanical and chemical stresses affecting stability	(Xiang and Cao, 2021; Xiang et al., 2017; Mawazi et al., 2024; Lombardo and Kiselev, 2022)
Microfluidic Methods	Microfabricated flow cells enable precise mixing of lipid and aqueous phases, forming uniformly sized nanoparticles.	• Precise control • High reproducibility, Reduced sample usage • Fast processing • High encapsulation efficiency	• Scalability issues • Complex design and fabrication • High initial setup costs, and maintenance required	(Mehraji and DeVoe, 2024; Agha et al., 2023; Maeki et al., 2015; Piunti and Cimetta, 2023)
Reverse-Phase Evaporation	Lipids in organic solvents form a reverse-phase emulsion, then sonication and solvent evaporation produce nanoparticles.	• High encapsulation efficiency • Versatility for various lipids and drugs • Controlled NPs size • Produces stable NPs with a long shelf-life	• Residual solvents may affect stability • Requires careful control • Potential drug degradation during evaporation.	(Cortesi et al., 1999; Shi et al., 2017)
Freeze-Thaw	Rapid freezing and thawing of lipid suspension break aggregates, forming uniform nanoparticles.	• Simple and cost-effective • High encapsulation efficiency • Easily scalable • No need for organic solvents	• Potential for drug degradation • Inconsistent particle size • Physical stress affecting stability	(Costa et al., 2014; Khayrani et al., 2024; Souri et al., 2023)
Detergent Removal	Lipids and proteins form micelles in detergent, then detergent removal creates lipid nanoparticles.	• Effective for membrane proteins • Versatile with various lipids and proteins • Allows for controlled detergent removal	• Technically challenging • Potential for protein denaturation • Time-consuming process	(John et al., 2024; Schubert, 2003; Schubert, 2003)
Emulsification followed by High-Pressure Homogenization (HPH)	Lipids are emulsified in an aqueous phase and then processed with HPH to reduce particle size and achieve uniformity.	• High encapsulation efficiency • Suitable for SLNs and NLCs • Scalable process	• Requires specialized equipment • High energy input • Potential size distribution variation	(Zhou et al., 2022; Vinchhi et al., 2021; Amasya et al., 2019)

of their high glucose utilization caused by the greater density of glucose transporter-1 (GLUT1). Glycosylated LPs were shown to be carried across the BBB by a combination of classical endocytosis and a distinct transcytosis pathway, as demonstrated by in vitro time-lapse live-cell imaging, flow cytometry, and in vivo near-infrared fluorescence imaging (Harbi et al., 2016).

Various enzymes found in blood, endothelial cells, BBB, and BBTB may also hinder NP-based drug delivery. Using proteolytically stable peptides, ^{D}CDX and c(RGDyK), one study group altered the liposome surface to bypass multiple barriers. On the BBB, ^{D}CDX binds to nicotine acetylcholine receptors (nAChRs), whereas c(RGDyK) binds to integrin, which is abundant on BBTB and glioma cells. The cellular uptake studies demonstrated that liposomes with dual tags were able to effectively cross the BBB and BBTB monolayers, circumvent the enzymatic barrier, and target 3-D tumor spheroids. Ex vivo imaging and histology testing provided additional confirmation of its ability to specifically target cerebral gliomas in living organisms. Compared to unmodified liposomes and liposomes modified with only one peptide ligand, liposomes modified with both ^{D}CDX and c(RGDyK) and containing doxorubicin (DOX) showed a more effective anti-glioma effect. This led to an increased median lifetime in nude mice with glioma (Fig. 6) (Wei et al., 2015).

To enhance liposome uptake into the brain, the positively charged surface of cationic liposomes interacts electrostatically with the negatively charged BBB, which in turn triggers liposome internalization by cells (Ross et al., 2018; Lan et al., 2024; Karimi et al., 2404).

Nanoparticles may develop homologous targeting and immune-escaping properties by adorning their surfaces with various cellular membrane proteins, in addition to active targeting ligands and PEG. Biomimetic NPs can achieve self-recognition via interactions between proteins on tumor cell membranes and the receptors on cells. When used in conjunction with other methods to breach the BBB, these multifunctional liposomes can greatly enhance the drug-delivery system's ability to reach the brain, leading to better diagnosis and therapy. Conventional liposomes, on the other hand, are quickly eliminated by the RES, resulting in quick systemic clearance. Liposomes that have been altered

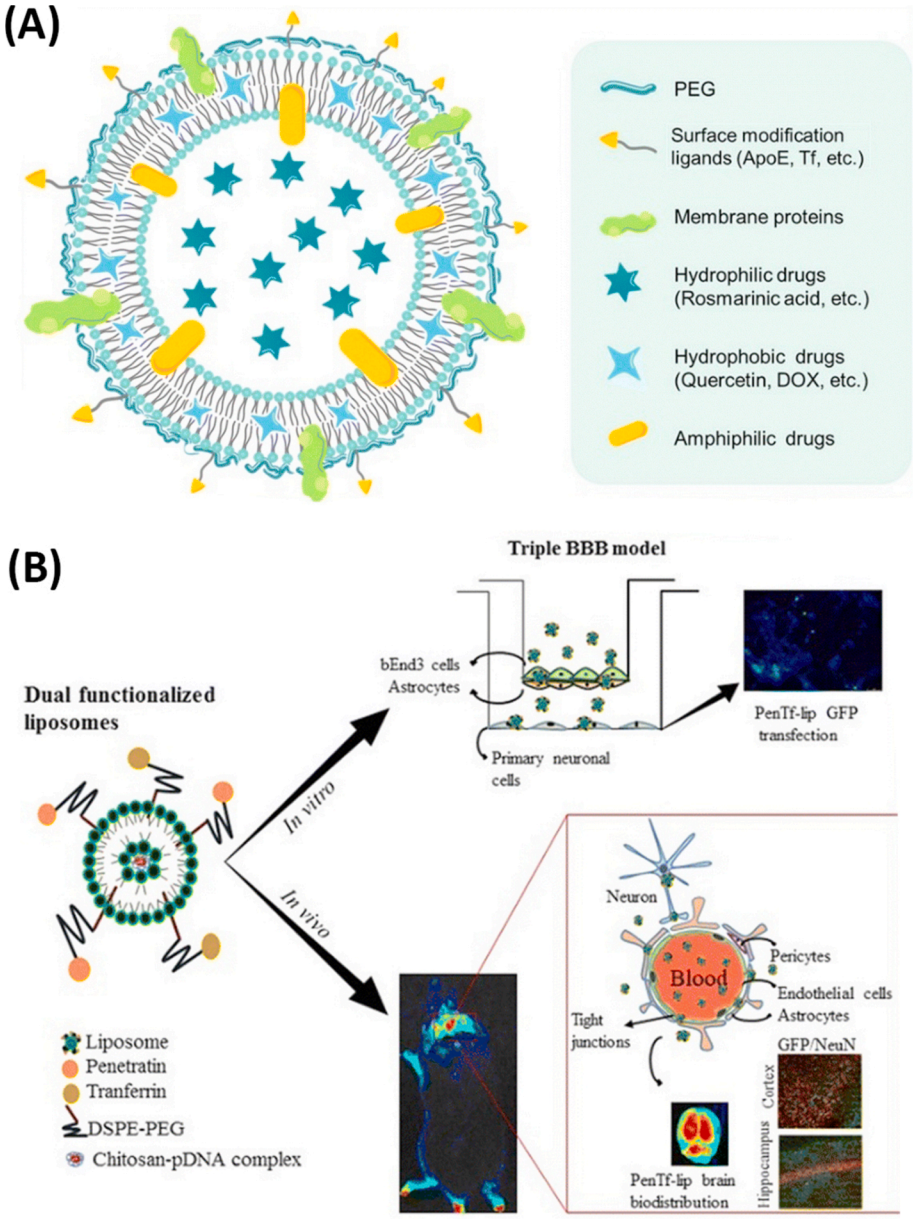


Fig. 5. (A) Illustration of a drug-loading liposome, Reprinted with permission from Tan et al (2022) (Tan et al., 2022). (B) Bifunctional liposomes as a vehicle for gene transfer, Reprinted with permission from Rodrigueset et al (2018) (dos Santos Rodrigues et al., 2018).

with hydrophilic PEG can avoid being captured by the RES, resulting in enhanced medication uptake in the brain (Alyautdin et al., 2014; Razavi et al., 2024).

Glu- and PEG-modified liposomes showed the best brain-targeting ability, according to Xie et al., who tested a range of PEG chain lengths (PEG200, PEG400, PEG1000, and PEG2000) and found that length of PEG chain significantly affects liposome brain-targeting efficiency (Xie et al., 2012). The presence of long polyethylene glycol (PEG) chains creates a steric barrier, whereas short PEG chains can shield glutamic acid (Glu) from being exposed. Liposomes were able to enter the brain by means of RMT, facilitated by the multivalent interaction between GLUT1 in brain capillary endothelial cells and Glu (Wang et al., 2022). A PEGylated liposome carrying DOX was modified by Zhang et al. with a cell penetration peptide (CB5005) (Zhang et al., 2018). With a diameter of about 110 nm, the produced liposomes exhibited typical spherical forms. The two primary functions of CB5005, which enable it to effectively enter gliomas and inhibit nuclear factor-κB (NF-κB) activity, are cell membrane penetration and NF-κB suppression. In addition to enhancing DOX's ability to kill U87 tumor cells, the CB5005 modification significantly boosted glioma cells' absorption of liposomes.

Nanoparticles can be made more targetable and increase their rate of brain uptake via RMT by conjugating liposomes with antibodies or ligands that are specific to the brain. The ability of ApoE to bind to BBB receptors like low-density lipoprotein receptors (LDLRs) and LDLR-related proteins (LRPs) is one such example. Encapsulating chemotherapeutic osthole (Ost) in Tf-modified and PEGylated liposomes (Tf-Ost-LP) was created by Cheng et al. for the treatment of AD (Kong et al., 2020). In a study conducted by Muzykantov et al., liposomes conjugated with vascular cell adhesion molecule 1 (anti-VCAM) showed superior accumulation in the brain when compared to liposomes coupled with TfR or intercellular adhesion molecule 1 (ICAM-1). With an intravenous injection, anti-VCAM-liposomes had an uptake efficiency 27-fold higher than TfR-1-liposomes and 8-fold higher than ICAM-1-liposomes in an inflammatory brain. This resulted in a brain/blood ratio that was 4300

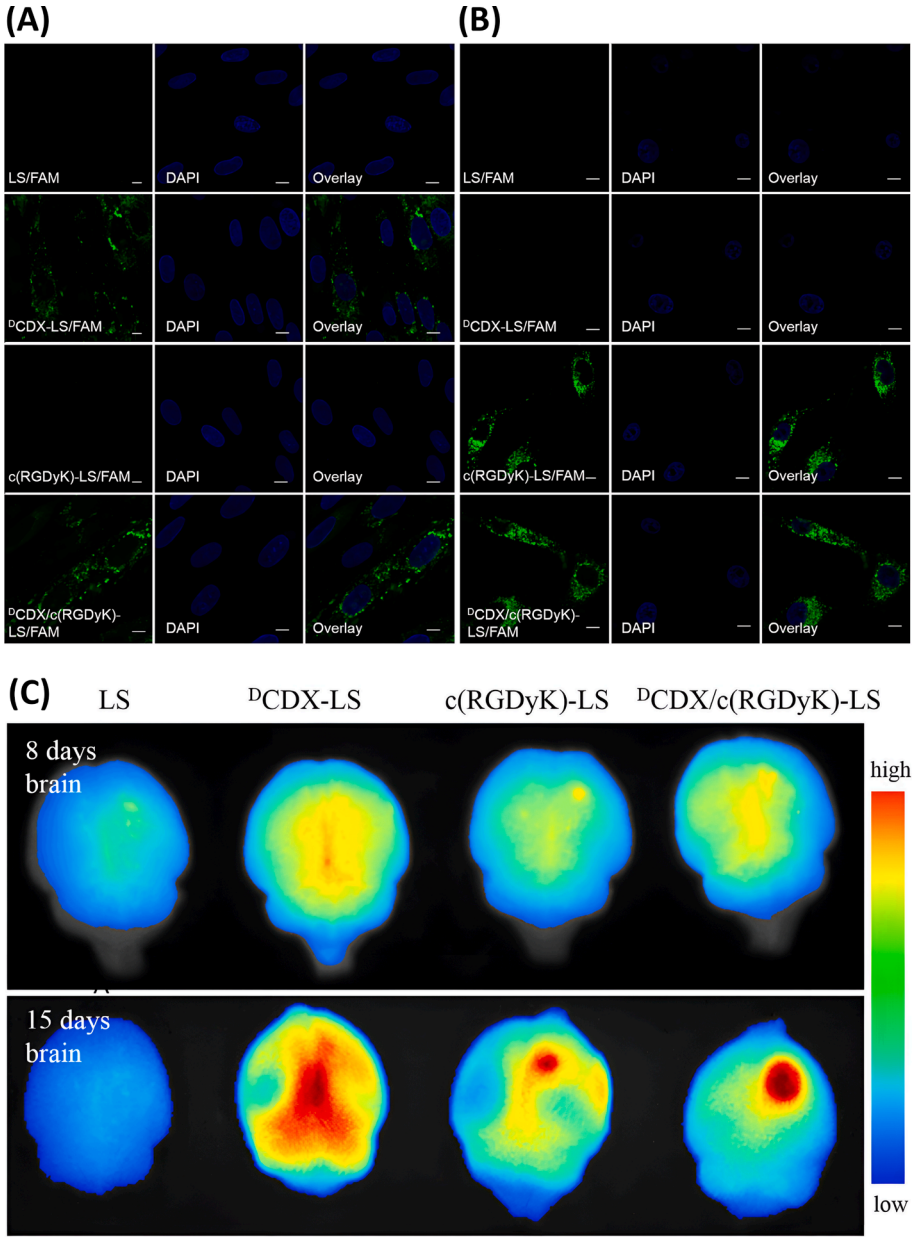


Fig. 6. A) Cellular uptake of liposomes by the primary BCESs and B) U87 cells. C) Over time, unmodified liposomes had a low brain distribution rate, but ^{D} CDX-LS, due to its capacity to target the BBB, had a widespread and nonselective distribution throughout the brain. Brain tumors, on the other hand, showed a small accumulation of c(RGDyK)-LS, Reprinted with permission from Zhao et al (2020) (Wei et al., 2015).

times higher than immunoglobulin G/liposomes (Marcos-Contreras et al., 2020). On the other hand, RMT is a kind of transport that may often reach saturation point. To increase delivery efficiency and circumvent receptor saturation, dual targeting is an effective strategy. Liposomes had two targeting functions: first, Pen, a cationic cell-penetrating peptide, could overcome receptor saturation, enhance intracellular delivery, and facilitate endosomal escape. Second, Tf could penetrate the BBB (dos Santos Rodrigues et al., 2018). The produced liposomes had round shapes and consistent particle sizes ranging from 147 to 167 nm. Moreover, the functionality of chitosan in protecting DNA from enzymatic degradation and enhancing transfection efficiency was assessed by developing a liposome encapsulation of the hydrophilic plasmid produced by galactosidase complexation (Fig. 5B). Encapsulation efficiency of 93 % was achieved with the liposomes when plasmid DNA (pDNA) containing green fluorescent protein was used. When tested in vitro after 8 h, Pen-Tf liposomes had a BBB penetration rate of 15.2 %, compared to 2.6 % for Pen and 3.5 % for Tf liposomes. In order to transport DOX and erlotinib to the brain, the researchers employed Tf and Pen-modified liposomes as dual targeting agents. The usage of Tf-Pen liposomes resulted in a 12-fold increase in DOX accumulation and a 3.3-fold rise in erlotinib accumulation in the mouse brain. The promise of Tf-Pen liposomes as a therapy for aggressive gliomas was further shown by the fact that mice treated with the compound had a longer lifetime and a smaller brain GBM compared to the control group (Lakkadwala et al., 2019; Soltani et al., 2021).

Liposomes provide a simple alternative to the more involved method of ligand modification for nanoparticles surface camouflage using proteins found in cell membranes. Plasmids that induce cell death in response to tumor necrosis factor were condensed using cationic micelles formed by vitamin E succinate-grafted ε-polylysine (VES-g-PLL) polymers. The VES-g-PLL micelles were located in the inner compartment of the liposomes, which contained egg lecithin and cholesterol, and the glioma cell membrane was surrounded by a lipid layer. A spherical-shaped (~ 130 nm) T@VP-MCL with a zeta potential of 14.9 mV was produced as a result (Zhao et al., 2020). Due to the fact that liposomes and endothelial cells undergo electrostatic adsorption, NP penetration is enhanced. Furthermore, by focusing on ICAM-1 in gliomas, the liposomes have the ability to modulate the expression of ZO-1 which is a TJ protein. The MRI scans unequivocally demonstrate that the tumor volume progressively increased in the control groups of rats, but the experimental group had a conspicuously reduced rate of tumor growth. The BBB can be temporarily opened by applying mechanical stress to the brain endothelium using a combination of microbubbles delivered throughout the body and low-intensity pulsed focused ultrasound (LIFU) (Hosseinpour et al., 2024; Moradi Kashkooli et al., 2023). It has been mentioned that a stable liposomal O^6-(4-bromothenyl) guanine (O^6BTG) derivative has been delivered using image-guided LIFU. The chemotherapy drug temozolomide (TMZ) can be overcome by an enzyme that can repair TMZ-induced toxic DNA. Liposomes, acting as pseudo-substrates, can lead to MGMT depletion. Compared to the untreated tissue in the contralateral hemisphere, the LIFU-treated area had a much higher concentration of dye-labeled liposomes (Papachristodoulou et al., 2019). In addition, Lin et al. devised a technique to deliver therapeutic genes commonly employed in Parkinson's disease gene therapy, namely glia-cell-line-derived neurotrophic factor and brain-derived neurotrophic factor, to the brain. This was achieved by combining liposomes carrying the genes with microbubbles, and subsequently utilizing ultrasound to facilitate the opening of the BBB (Lin et al., 2020). The findings indicated that the use of ultrasound helped to overcome the BBB, resulting in improved delivery of genes and drugs into brain tissue. This, in turn, facilitated the treatment of CNS problems.

To lessen the probability of pre-leakage, there are alternative liposome kinds that could regulate the release of drugs in the brain. One such type is temperature-sensitive liposomes (TSLs). Because of their phase-change capability at high temperatures, TSLs have applications in thermal stimulation-induced controlled drug release. Liposomes undergo a phase shift at temperatures above 40 °C, causing them to rupture and release the enclosed drugs. The TSLs utilize intravascular triggered wrapped drug release, wherein the medication is released as liposomes pass through heated tissue. Drugs may be released from some TSL formulations in a matter of seconds. Faster drug release is achieved with higher temperatures or longer heating times. Heat stimulation also aids in opening the BBB, allowing TSL to traverse the portion of the BBB that is momentarily disturbed and reach brain tissue (Bredlau et al., 2018; Razavi et al., 2024). A TLS system with dual-function activity was created by Shi et al. to encapsulate medications (Shi et al., 2019). The liposomes' outside membrane was conjugated with a GBM cell-penetrating peptide and an anti-GBM antibody to enable precise delivery to GBM cells. Subsequently, the liposomes were filled with DOX and superparamagnetic iron oxide NPs (SPIONs) (Souri et al., 2022; Souri et al., 2021). Although they had no discernible effect on the activity of normal brain cells, the dual-function liposomes outperformed non-functionalized liposomes in inhibiting tumor cell growth and increasing entrance into U-87 human GBM cells.

The examples given above demonstrate that the therapeutic effectiveness against CNS illnesses, the reduction of undesirable effects, and the increase of blood circulation half-life are all improved by liposomal medicine encapsulation. Nevertheless, the composition of the liposome can be influenced by a range of chemical, physical, and biological factors, including the qualities of the phospholipid components, the solvent used, the techniques of synthesis, the temperature, and the speed of stirring during storage, manufacture, and application. These characteristics need more research prior to their clinical use since they directly impact the stability of drug-carrying liposomes and their biological activities.

3.1.2. Solid lipid NPs

Due to their advantageous properties, solid lipids were chosen as a substitute for liquid lipids. SLNs have the ability to encapsulate or embed drugs due to the presence of a lipid core. These particles are solid colloidal structures made up of natural or synthetic solid lipids such as lecithin and triacylglycerol (Tapeinos et al., 2017). Three models exist for drug incorporation in SLNs (Müller et al., 2002): the solid solution model, the drug-enriched shell model, and the drug-enriched core model. The medicine is distributed evenly in a lipid matrix inside the homogenous matrix of solid solutions. The solid solution-model SLNs make use of drug compounds that bind strongly with lipids. Cold homogenization procedures are often used for their production (Üner and Yener, 2007). In the second form, known as the drug-enriched shell, the drug is incredibly concentrated in the outermost portion of the lipid NPs. During the process of recrystallization in shell-type SLNs containing drugs, a lipid core is formed, with the drug being highly concentrated in the outer shell (Das and Chaudhury, 2011). The drug-enriched core model, sometimes referred to as core–shell NPs, is the final and third model. Drug-lipid core–shell nanoparticles are created when the lipid forms a central core during the process of drug crystallization (Li et al., 2009). Erel-Akbaba et al. developed a nanoparticles called f(SLN)-iRGD by using microemulsion dilution technique and conjugating it with a cyclic peptide called iRGD. This nanoparticles combines small interfering RNAs (siRNAs) targeting the epidermal growth factor receptor (EGFR) and programmed cell death protein 1 (PD-1) in order to effectively target GBM for combined targeting and immunotherapy (Erel-Akbaba et al., 2019). While EGFR is the receptor that causes tumors to grow and metastasize aggressively, PD-1 can suppress the immune system by preventing T cells from proliferation and becoming activated (Erel-Akbaba et al., 2019; Shen et al., 2016; Ribas and Wolchok, 2018). Upon reaching tumor cells, the f(SLN)-iRGD employs RMT to infiltrate the cells or utilizes radiation to improve targeting and transport NPs to the tumor cells. In addition to altering permeability and the structure of endothelial cells, radiation therapy, lowers the pressure of tumor interstitial fluid, and influences the behavior of macrophages associated

with tumors at the peripheral tumors and in cases of vascular rupture. These changes facilitate f(SLN)-iRGD being delivered to the tumor efficiently (Erel-Akbaba et al., 2019; Miller et al., 2015). As f(SLN)-iRGD enters tumor cells, it can undergo pH changes in lysosomes and endosomes, causing SLN to interact with endosomal lipid membranes which are negatively charged, leading to siRNA release into the cytoplasm (Resnier et al., 2013; Niaki et al., 2020).

Slow-release medication regulation, enhanced physical and chemical stability, protection against degradation, enhancement of drug targeting to the brain, and bypass of efflux transporters (such as P-gp) are all mentioned as advantages of SLN utilization. Adding surfactants to SLNs makes them more stable, and some of those surfactants may even block P-gp, which means that medications may accumulate in the brain more quickly. Physical and chemical stability are both improved in SLNs as compared to liposomes.

SLNs may be administered in a variety of ways, including intravenously, subcutaneously (Zhao et al., 2020), ocularly, and via the pulmonary system (Zhao et al., 2017) Fig. 7A. The 83–14 monoclonal antibody was used by Kuo et al. as a modifier to create SLNs that loaded saquinavir (SQV) (Fig. 7B) (Kuo and Ko, 2013). The surfactants poloxamer 407 (P407, PEO-PPO-PEO) and polysorbate 80 (Tween 80), which contain several poly(ethylene oxide) (PEO) groups, were coated on the outer layer to enhance metabolic stability and brain accumulation. DSPE-PEG2000 was then applied to the coating. With its ability to bind specifically to the α-subunit of the human insulin receptor (hIR), the 83–14 monoclonal antibody may be used as a vector for brain targeting. Adsorption of ApoE, which is identified by LDLRs, onto the surface of the NPs using tween 80 enables the NPs to permeate the brain endothelial cells through RMT. Blocking P-gp efflux activity on human brain microvascular endothelial cells (HBMECs) was another effect of Tween 80. In summary, to enhance endocytosis and SLN entrance into HBMECs, SQV-SLNs were combined with Tween 80 and the 83–14 monoclonal antibody. In another research, Graverini et al. utilized Compritol 888 ATO, which is a combination of mono-, di-, and tri-glycerides of behenic acid, as the solid lipid, and Brij 78, a surfactant which is derived from stearic-acid molecules covalently conjugated to PEG1000, to create SLNs through an emulsification/evaporation/solidification technique. The SLN encapsulation of andrographolide (AG) had an impressive 92 % efficiency (Graverini et al., 2018). Not only clearance by the liver and RES, opsonization, and phagocytosis can be lowered, but also shielding NPs from plasma interference and extending their lifespan in the bloodstream can be caused by Brij 78. In addition, the formulation enhanced drug penetration across the neurovascular junction and protected NPs against attacks by astrocytes and pericytes due to its high lipophilicity and charge. The permeability of the hCMEC/D3 cell monolayer increased to $26.8 \pm 4.17 \times 10^{-6}$ cm s^{-1} after with NaF and 80 μM AG-loaded SLNs for 1 h, which is almost three times higher than the permeability of free AG.

As another approach, enhancement of BBB-bypassing capability by decoration with bioactive compounds is possible. For instance, ApoE-DON-SLNs, which contain donepezil and rhodamine B, were modified by Topal et al. to increase their permeability across the BBB (Topal et al., 2020). When compared to non-targeting liposomes, the uptake of ApoE-DON-SLNs by endothelial cells was more than four times greater after 2 h of incubation. For another instance, the warm micro-emulsification technique was also used to create SLNs with an ApoE-derived peptide (SLN-mApoE) as a ligand that specifically targets the brain. To determine how different routes of administration affected the brain bioavailability of SLN-mApoE, Magro et al. conducted an investigation (Dal Magro et al., 2017; Domenicucci et al., 2015). Subsequently, at different time intervals, the distribution of SLN-mApoE in the body was evaluated. After the intraperitoneal injection, the brain did not show any fluorescence, however the abdominal cavity exhibited noticeable fluorescence from SLN-mApoE, as shown in Fig. 7C. The brain fluorescence signal exhibited a percentage of 0.15 % three hours after the intravenous injection of SLN-mApoE, and decreased to 0.06 % after 24 h. Conversely, there was an absence of an early inflammatory reaction in the lungs following the administration of SLN-mApoE by pulmonary injection.

Depending on the makeup of the lipids and surfactants, SLNs can be broken down by lipolytic enzymes or pancreatic lipase. While steric stabilization is crucial for surfactant degradation (Yang et al., 1999; Olbrich et al., 2002), lipid degradation is length-dependent, with longer chains resulting in a slower breakdown. The ability of SLN to traverse the BBB is attributed to its lipophilicity and associated positive charge.

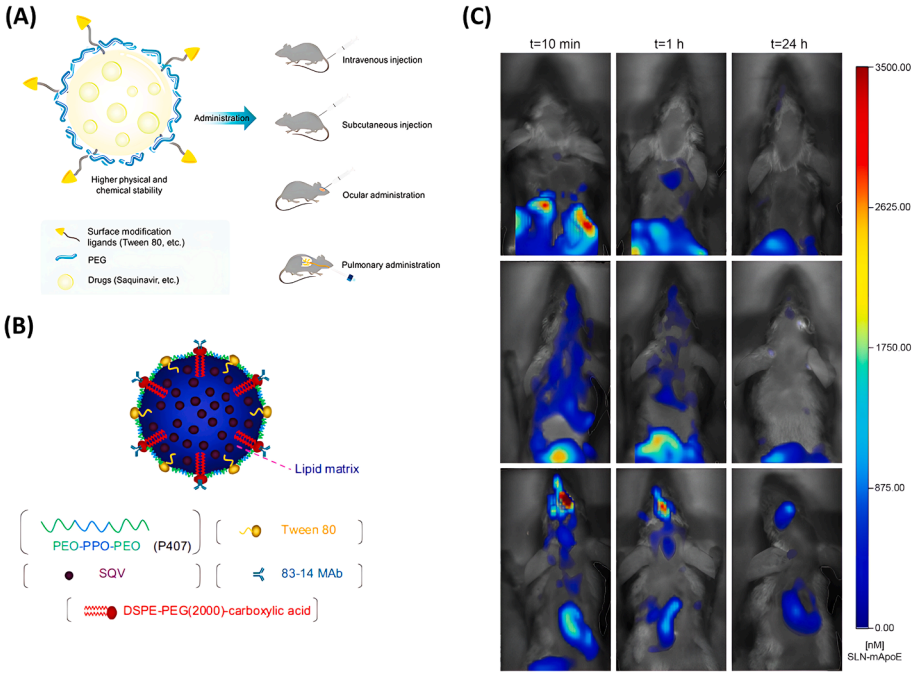


Fig. 7. (A) A schematic illustrating SLN and its several administrations, Reprinted with permission from Tan et al (2022) (Tan et al., 2022). (B) Schematic structure of an 83–14 MAb/SQV-SLN, Reprinted with permission from Kuo et al (2013) (Kuo and Ko, 2013). (C) Biodistribution of DiR-loaded SLN-mApoE in mice, Reprinted with permission from Dal Magro et al (2017) (Dal Magro et al., 2017).

The highly organized structure of the SLN lattice leads to limited drug loading and efflux capabilities, despite SLN's several benefits. Additionally, SLNs have a high aqueous dispersion (over 70 %) (Nsairat et al., 2021). Hence, to overcome these issues nano-structured lipid carriers have been created by the researchers.

3.1.3. Nano-structured lipid carriers

When compared to SLNs, which have poor drug loading and slow drug release due to the solid lipid's crystalline character, nano-structured lipid carriers (NLCs) with a mixture of liquid and solid lipids that create partially crystallized lipid systems are preferable. The liquid lipid phase can include molecules like oleic acid and medium-chain triglycerides, whereas the solid lipid phase is made up of triglycerides, fatty acids, waxes, etc. Curiously, by modifying these residues, different drug-release devices can be generated (Das and Chakraborty, 2015).

Compared to SLN, NLC has lower toxicity, greater stability, and more efficient encapsulation due to the unique physicochemical characteristics of the lipid combination. Nevertheless, sensitivity, irritation, or cytotoxicity might occur depending on the kind and concentration of NLC surfactant. Due to its tiny size and excellent biocompatibility, NLC can utilize many transport methods to enhance drug pass across the BBB. These include passive diffusion via paracellular and transcellular routes, as well as a path to circumvent the BBB and enter the brain by nasal delivery (Agrawal et al., 2020; Missori et al., 2010; Rinalduzzi et al., 2016). On one hand, NLC increases permeability by inducing the opening of TJs of the BBB; on the other, surface surfactants or permeability enhancers of NLC can dissolve endothelial cell lipids, facilitating transcytosis. In addition, NLC can enhance active drug transport through RMT when its surface is modified with ligands that specifically target the desired receptors. This link improves the interaction between drug transporters and receptors specific to the BBB. Substances administered through nasal injection can enter the brain either through the olfactory pathway or by circulating through the respiratory region. For the treatment of glioma and brain cancer, NLC may be paired with several medications to build co-delivery systems. As examples of such a system, the dual drug TMZ and vincristine NLC co-delivery system (Bothun et al., 2011; Wu et al., 2016), Tf-modified NLC loaded with artemisinin (Koo et al., 2006), Tf-modified NLC loaded with pertussis toxin (PTX) (Emami et al., 2017), TMZ-loaded NLC (Alam et al., 2012), curcumin-loaded NLC (Chen et al., 2016) and polysorbate 80-coated NLC (Sharma et al., 2011) can be mentioned.

The use of NLC for co-delivery enhances targeting and accelerates the process of inhibiting tumor development due to the positive surface charge of the material, which attracts the system to the negatively charged tumor cells (Lu et al., 2019). As demonstrated in Fig. 8, the anti-tumor effectiveness was evaluated utilizing PET/MRI analysis. A targeted delivery method was created in 2022 by Farshbaf et al. using dual NLCs, which are NLCs modified with two proteolytically stable D-peptides, D8 and RI-VAP. D8 can efficiently cross the BBB and bind to the overexpressed nAChRs on BCECs (Farshbaf et al., 2022; Missori and Currà, 2015). RI-VAP possesses enhanced glioma-targeting capabilities, allowing it to circumvent the BBTB to selectively attach to cell surface GRP78 (csGRP78), a biomarker present on both angiogenic and cancerous cells. Dual NLCs shown higher efficacy in penetrating in vitro BBB and BBTB models and internalizing tumor neovascular endothelial cells, glioma cells, and BCECs, as compared to non-targeted or mono-targeted NLCs. During the experiment on mice with glioma, the combination of dual NLCs/Bortezomib (BTZ) resulted in higher levels of medication at the tumor site. This led to improved quality of life and enhanced survival in the mice with glioma, indicating promising therapeutic outcomes. Due to the overall improvement in the therapeutic efficacy of hydrophobic anti-glioma chemotherapeutics, dual NLCs may therefore serve as a suitable alternative to the present approaches used to treat brain cancer. The Table 5 provides an overview of NLCs and SLNs that have been produced lately with the purpose of brain targeting.

3.2. Polymer-based NPs

3.2.1. Chitosan

Chitosan, a polymer with numerous medicinal uses, is commercially produced from shrimp shells. Chitosan NPs can be synthesized using various methods, such as ionic gelation, microfluidics combined with the microemulsion technique, and ion gelation with TPP as a cross-linking agent (Van Bavel et al., 2023; Tenorio-Barajas et al., 2023; Thirugnanasambandan and Gopinath, 2023). The synthesis process involves creating monodisperse NPs with controlled sizes, typically ranging from 15 nm to 80 nm, depending on the method used (Costa et al., 2023). Table 6 is a summary that compares the advantages and disadvantages of different synthesis methods.

The ability of chitosan nanoparticles to pass through biological barriers makes them valuable for delivering complex drugs, such as insulin, vaccines, plasmid DNA, and genes. Chitosan-based nanoparticles (CsNPs) have the ability to interact with endothelial cells through ionic interactions. This interaction enables the transport of drugs across the BBB by utilizing adsorptive mediated transcytosis (Caprifico et al., 2020). Various chemical modifications, such as acylation, tosylation, or O-carboxymethylation, as well as functionalization with antibodies, ethers, or lipids, can be developed to improve the efficacy of chitosan to penetrate the BBB. The functional groups found in chitosan, such as amino, primary, and secondary hydroxyl groups, make this feasible (Fig. 9). The utilization of N-TMCs resulted in the application of a coating on solid lipid NPs, resulting in a significant enlargement of the nanoparticle size from 138 nm to 412 nm, which indicates the successful completion of the coating process. This innovative drug delivery system aimed to enhance the oral delivery of curcumin, specifically targeting the brain for treating AD and gliomas. Curcumin was loaded into NPs, and the distribution of the NPs after being taken orally was evaluated by in vivo trials conducted on mice. The findings demonstrated that the bioavailability of curcumin was enhanced when it was encapsulated in SLNs coated with N-TMC. This indicates that the coating effectively shielded curcumin from degradation in the gastrointestinal tract. Agyre et al (Agyare et al., 2008). applied a layer of a biosensor capable of detecting amyloid deposits on the surface of CsNPs. These deposits are found on the blood vessels in the brain and the brain tissue itself. Amyloid deposits are the primary cause of AD and cerebral amyloid angiopathy. The F(ab')2 portion of Aβ antibody (IgG4.1), which has been altered with putrescine, is referred to as pF(ab')24.1 (pF). This pF fragment was used to coat NPs because it has the ability to traverse the BBB and attach to the amyloid deposits. Gu et al (Gu et al., 2017) employed dual ligand-modified CsNPs to transport therapeutic genes, specifically siRNA, for the purpose of suppressing immunodeficiency virus (HIV) infection in astrocytes. The chitosan underwent modification with two antibodies, namely the anti-Tf-R antibody for the purpose of selectively targeting cerebral endothelial cells, and the human bradykinin B2 receptor (B2-R) antibody for the purpose of selectively targeting astrocytes.

CsNPs are generally used in biomedical fields for drug and gene delivery into tumors, including applications in cancer therapy and tissue engineering, showcasing their versatility and effectiveness in brain-related treatments. (Jha and Mayanovic, 2023; Karimi Rouzbahani et al., 2024; Valizadeh et al., 2024). these applications are discussed in Table 7.

Chitosan NPs can be a potential carrier for the sustained delivery of the anti-Alzheimer drug rivastigmine (RT), offering improved bioavailability and efficacy for the treatment of AD and Parkinson's disease. Raja et al (Raja et al., 2021). found that formulating and evaluating chitosan NPs loaded with RT can cause sustained release and enhanced penetration of the BBB. The results showed that loading the drug within the NPs reduced the particle size, and the highest drug entrapment efficiency was achieved with a 4 % chitosan concentration.

Chitosan NPs can be used for non-invasive imaging of brain tissues, aiding in the diagnosis and monitoring of neurological disorders. In

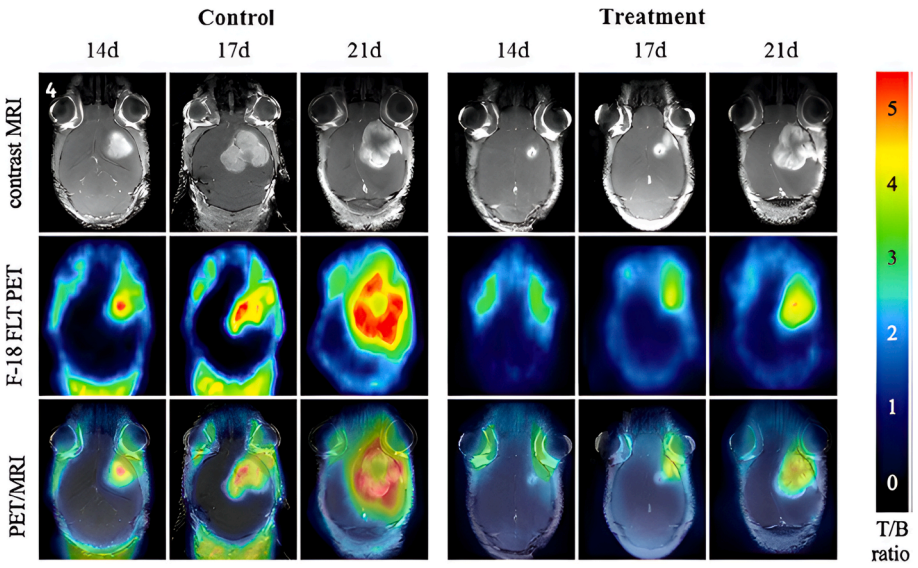


Fig. 8. Evaluation of antitumor efficacy using PET/MRI analysis. At 14, 17, and 21 days after U87 cell implantation, results are shown for tumor-bearing nude mice in the control group (TML-CET) and the treatment group (TML-CPT-11-CET with magnetic guidance + AMF treatment), Reprinted with permission from Lu et al (2019) (Lu et al., 2019).

Table 5
Recent Formulations of SLNs and NLCs for Enhanced Brain Drug Delivery.

Type of nanoparticles	Composition	Surface modification	Target moiety	Drug	Obtained results	Reference
SLNs; NLCs	Cetyl palmitate, Tween 80 Cetyl palmitate, Miglyol-812, Tween 80	RVG29 peptide (conjugated to DSPE-PEG2000-MAL)	nAChR	Quercetin	Significantly higher quercetin EE% (>80 %), superior permeability across the BBB compared to non-functionalized NPs, and neuroprotective characteristics	(Pinheiro et al., 2020)
SLNs	Glyceril monostearate, stearic acid, soya lecithin, Tween 80	Angiopep-2	LRP 1	Docetaxel	Longer circulation compared to free drug; enhanced cellular uptake and cytotoxicity	(Kadari et al., 2018)
NLCs	Compritol 888 ATO, MCT 812, Myrj 52, soy lecithin, mPEG-MAL mPEG-OH	Monoclonal antibody OX26	TfR	Salvianolic acid B, Baicalin	Increased bioavailability and better drug absorption by RME	(Wu et al., 2019)
SLNs	Cetyl palmitate, Tween-80	β-hydroxybutyric acid-stearyl amine conjugate	MCT-1 receptor	Carmustine temozolomide	Enhanced anticancer efficacy compared to free drugs; better absorption into the brain	(Ak et al., 2021)
SLNs	Dynasan 116	ApoE	LDLR	Donepezil	Superior absorption by the brain compared to uncoated NPs	(Topal et al., 2020)
	Tween 80	DSPE-PEG-avidin	LRPs		Compared to normal SLNs, ApoE-SLNs penetrate a BBB model at a rate two times greater.	
SLNs; NLCs	Cetyl palmitate, Tween 60, Cetyl palmitate, Tween 60, Miglyol-812	Transferrin, (conjugated to DSPE-PEG(2000)–NH_2)	TfR	Curcumin	Permeability testing on hCMEC/D3 cells revealed 1.5-fold improvement in curcumin absorption across the BBB. permeability study on hCMEC/D3 cells	(Neves et al., 2021)
NLCs	Palmityl palmitate Miglyol 812 SPC, Solutol HS15	Lactoferrin (Lf) DSPE-PEG2000-COOH	LDL	Nimodipine	The LF-RME method of intracellular administration was successful in a model of stroke cells.	(Zhao et al., 2018)
SLNs	Sodium behenate, polyvinyl alcohol 9000/12000	Transferrin, insulin, ST-MBS/ST-PEG- MBS linker	TfR; IR	Dodecyl-methotrexate	PEGylated functionalized SLNs were able to traverse the BBB	(Muntoni et al., 2019)

2022, Liu et al (Liu et al., 2022) fabricated novel hybrid nanogels, referred to as CTS/TPP/PAA@AuNPs (CTPA), as theranostic nanoparticles. The CTPA nanogels facilitate the entry of DOX into the cytoplasm and enable favorable accumulation in the tumor, as visualized through AuNPs-mediated CT imaging (Fig. 10A). Utilizing the natural polymer chitosan in nanogels is a beneficial approach for creating sophisticated theranostic systems. Sepasi et al (Sepasi et al., 2023) have shown that glioma cells absorbed CS-PEG-CDX/pEGFP NPs in a dosage-dependent manner. Through in vivo imaging, it was seen that the nanocomplexes effectively penetrated the brain tissue, as evidenced by the presence of green fluorescent protein (GFP) acting as a marker. In order to evaluate the effectiveness of the nanocomplexes in reaching the brain, EtBr-labeled pEGFP/CS-PEG-CDX and EtBr-labeled pEGFP/CS nanocomplexes were injected into mice intraperitoneally. The injections were administered daily for a continuous period of 5 days, with each animal receiving a dosage of 50 μg DNA. The weight ratio between nanocomplexes and plasmids was consistently maintained at a ratio of 10:1. Each injection administered daily had a volume of 200 μl. Following a period of 5 days, the mice were euthanized, and several organs, such as the heart, spleen, kidneys, liver, and brain, were extracted to evaluate the dispersion of the nanocomplexes throughout the body. Fig. 10B depicts the identification of Ethidium bromide-labeled pEGFP in the brain of the animal that was administered Ethidium bromide-labeled pEGFP/CS-PEG-CDX, in contrast to the control group. The presence of NPs in important organs such as the liver, spleen, heart, and kidneys was identified. Fig. 10C illustrates that the

Table 6
Various methods of Chitosan nanoparticle synthesis.

Synthesis Method	Description	Advantages	Disadvantages	Ref
Ionotropic Gelation	Chitosan is dissolved in an acidic solution and mixed with TPP or STPP under stirring, causing ionic gelation and forming spherical particles via charge complexation.	• Simple and mild reaction conditions • Ability to produce chitosan NPs with different characteristics by varying parameters like chitosan and crosslinker (TPP) concentrations • Produces NPs with narrow size distribution and high stability • Can be used to encapsulate active compounds like Aloe vera	• Potential for NP agglomeration if not properly optimized • Requires the use of a crosslinker (e.g., TPP) which may affect the properties of the NPs	(El-Kemary, 2022; Ismik et al., 2019; Worawong and Onreabroy, 2023)
Emulsion Crosslinking	Chitosan's amine groups cross-link with aldehydes (e.g., glutaraldehyde) to stabilize polysaccharide droplets, followed by washing and drying to remove excess reagents.	• Produces small, uniform NPs • Good encapsulation efficiency for hydrophilic drugs	• Use of organic solvents • Potential for residual surfactants	(Jafernik et al., 2023; Mikušová and Mikuš, 2021)
Top-down method	Chitosan nanoparticles and nanofibers were produced from deacetylated chitin nanofibers via chemical, mechanical treatments, and ultrasonication.	• Natural source	• high temperature	(Younes and Rinaudo, 2015)
Reverse Micellar	Reverse micelles are formed by dissolving surfactant in an organic solvent. Chitosan NPs are created within the micelle core, leading to an aqueous phase.	• Produces small, uniform NPs • Good encapsulation efficiency for hydrophobic drugs	• Use of organic solvents • Complex process with multiple steps	(Janes et al., 2001)

spleen is the primary location where EtBr-labeled pEGFP/PEG-CDX interacts.

3.2.2. *Dendrimers*

Dendrimer NPs have a complex, tree-like structure with well-defined branches (Fig. 11). Dendrimers are an emerging class of core–shell polymers that can be accurately manufactured at the nanoscale for a variety of uses. There are many different kinds of dendrimers, and some of them with their application are listed in Table 8.

Dendrimers can be synthesized using two techniques:

- Divergent: divergent involves incremental growth from a central core, yielding significant output. This method is used to manufacture PAMAM dendrimers and poly(propyleneimine) dendrimers. Highly pure dendrimers can be manufactured via the divergent approach, which involves size-exclusion chromatography (Esumi and Antonietti, 2003).
- Convergent: convergent synthesizes dendrimers from the outermost layers to the central core, ensuring a consistent number of reaction sites. Convergent dendrimers can produce flawless ones without defects (Esumi and Antonietti, 2003).

Overall, both divergent and convergent synthesis techniques have a significant impact in the production of dendrimers with specific properties and characteristics.

Dendrimers' ability to traverse cellular membranes, including the BBB, makes them promising drug delivery options (Abou El-Nour et al., 2010). Dendrimer nanoparticles are increasingly significant in the field of biomedical applications. Some of these applications are listed in Table 9.

Posadas et al (Posadas et al., 2022) showed that phosphorous dendrimers protect neurons by blocking NMDA-mediated excitotoxic mechanisms in rat cortical neurons. These mechanisms include lowering calcium levels inside neurons, stopping mitochondrial potential collapse, lowering free radicals, stopping caspase activation, and stopping endoplasmic reticulum stress.

Gold nanostars having plasmonic properties, when combined with peptide dendrimers (H3/H6) that were specifically designed, demonstrated promise as neuroprotective agents and had interactions with neurons (Souri and Soltani, 2024). They traversed the BBB, attached to zzplasma membranes, and stimulated the growth of neurites. Morfill et al (Morfill et al., 2022) demonstrated that H3-AuNPs (star-shaped gold nanoparticles) provided protection to neurons against oxidative stress and cytotoxicity associated with Parkinson's or AD and that H3-AuNS exhibited more potency compared to H3-AuNP. These findings suggest that H3-AuNS has the potential to be a highly effective treatment for neurodegenerative illnesses, providing a fresh approach to therapy. The ability of these gold nanostars to interact with neurons and provide protection against endoplasmic reticulum stress further underscores their potential in combating neurodegenerative disorders. Continued research in this area may lead to the development of innovative therapies that target the underlying mechanisms of these debilitating conditions. Also, unconjugated S100A4 motifs, which are part of the dendrimers, slowed down neurodegeneration caused by Aβ, which suggests that they may play a part in AD (Fig. 12).

Xu et al (Xu et al., 2016) examined the ability of folic acid (FA)-conjugated polyamidoamine dendrimer G4 (G4-FA) to specifically deliver genes to head and neck cancer cells, which are known to have high levels of folate receptors (FRs). The study evaluated the effectiveness of G4-FA in transferring genes into HN12 cells in a laboratory setting, using GFP and YFP plasmids as markers. In order to assess the potential enhancement of gene transfection, the researchers conducted a comparative analysis between G4-FA, a targeting moiety, and non-targeting G4, as well as alternative techniques. G4-FA clearly outperforms non-targeting G4 in terms of both the total amount of gene expression and the proportion of transfected cells. This conclusion is

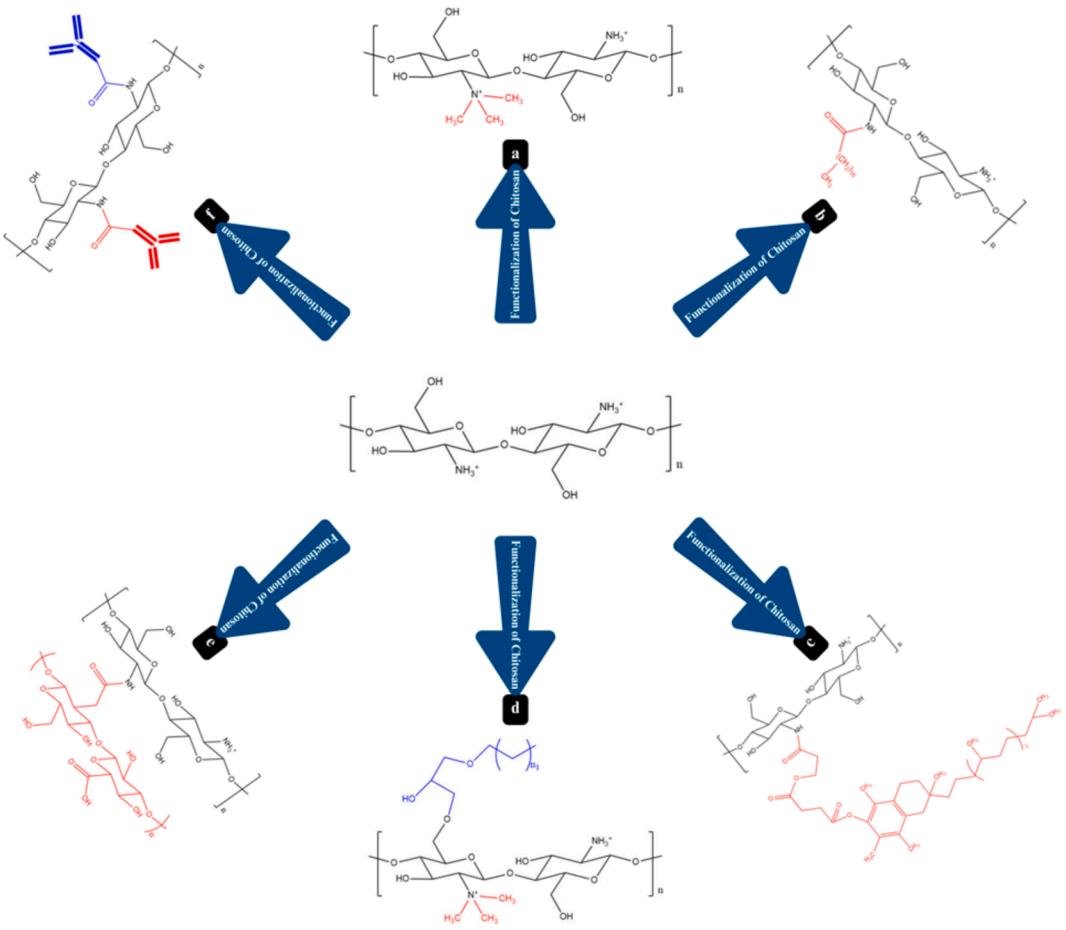


Fig. 9. The structure of chitosan functionalized with a) Tri methylated. b) stearic acid. c) d-α-tocopherol PEG. d) alkyl glycerol and Tri methylated. e) hyaluronic acid. f) two different antibodies.

Table 7
Summary of in vivo and in vitro studies Utilizing chitosan nanoparticles.

Drug delivery	**Nanoparticles**	**Application**	**model**	**Results**	**Ref**
	Chitosan-coated SeNPs (Cs-SeNPs)	cancer therapy	In vitro	Chitosan-coated selenium NPs (Cs-SeNPs) outperformed SeNPs in suppressing glioma cell growth, enhancing 5-FU sensitivity, and penetrating the BBB.	(Dana et al., 2022)
	CDX-modified chitosan NPs (CS-PEG-CDX NPs)	Gene therapy	In vivo and in vitro	CS-PEG-CDX NPs were synthesized for brain gene delivery, showing dose-dependent uptake by glioma cells in vitro and successful brain infiltration in vivo, confirmed by GFP markers.	(Serap et al., 2022)
Theranostic	CTS/TPP/PAA@AuNPs (CTPA),	computed tomography (CT) and Tumor Chemotherapy	In vivo	CTPA@DOX showed strong tumor accumulation, effective AuNP conjugation, and self-monitoring capabilities for drug administration.	(Liu et al., 2022)

derived from the findings acquired through western blottin and flow cytometry analysis. Specifically, the use of G4-FA resulted in a 72 % increase in protein expression and a 250 % improvement in GFP-positive HN12 cells when combined with plasmid at a ratio of 5:1. The study determined that the effectiveness of G4-FA in transferring genetic material was influenced by the ratio at which it was coupled with plasmids. The highest level of efficiency was observed when G4-FA and plasmids were combined at a weight ratio of 5:1.

3.2.3. Nanogel

Nanogels are three-dimensional structures made of physically (Dependence on physical interactions, such as hydrogen bonding, electrostatic forces, van der Waals interactions, and hydrophobic interactions, characterize the formation of nanogels.) or chemically crosslinked (utilizes covalent bonds) polymers with hydrophilic or amphiphilic macromolecular chains. These chains can absorb large amounts of water without dissolving or otherwise changing their shape, allowing the nanogels to swell. Along the macromolecular chains of the polymer, hydrophilic functional groups like OH, CON, CONH, and SO_3H. This is what makes it so good at absorbing water. The techniques employed in the synthesis of nanogels are of utmost importance in establishing the physicochemical characteristics, structure, and functioning of the resultant NPs. Over the years, a wide range of synthetic approaches has been developed, each offering distinct advantages and limitations. These methods can be broadly categorized into chemical and physical approaches, depending on the mechanism of nanogel formation and the nature of the interactions involved in crosslinking polymer chains or assembling NPs. Some of these methods are listed in Table 10.

Nanogels possess key characteristics that enable them to cross the BBB. These characteristics include their nanoscopic size (20–200 nm), high drug-loading capacity, responsiveness to environmental stimuli like pH, temperature, redox (Zhao et al., 2021), and the ability to encapsulate a wide range of therapeutics, from small molecules to

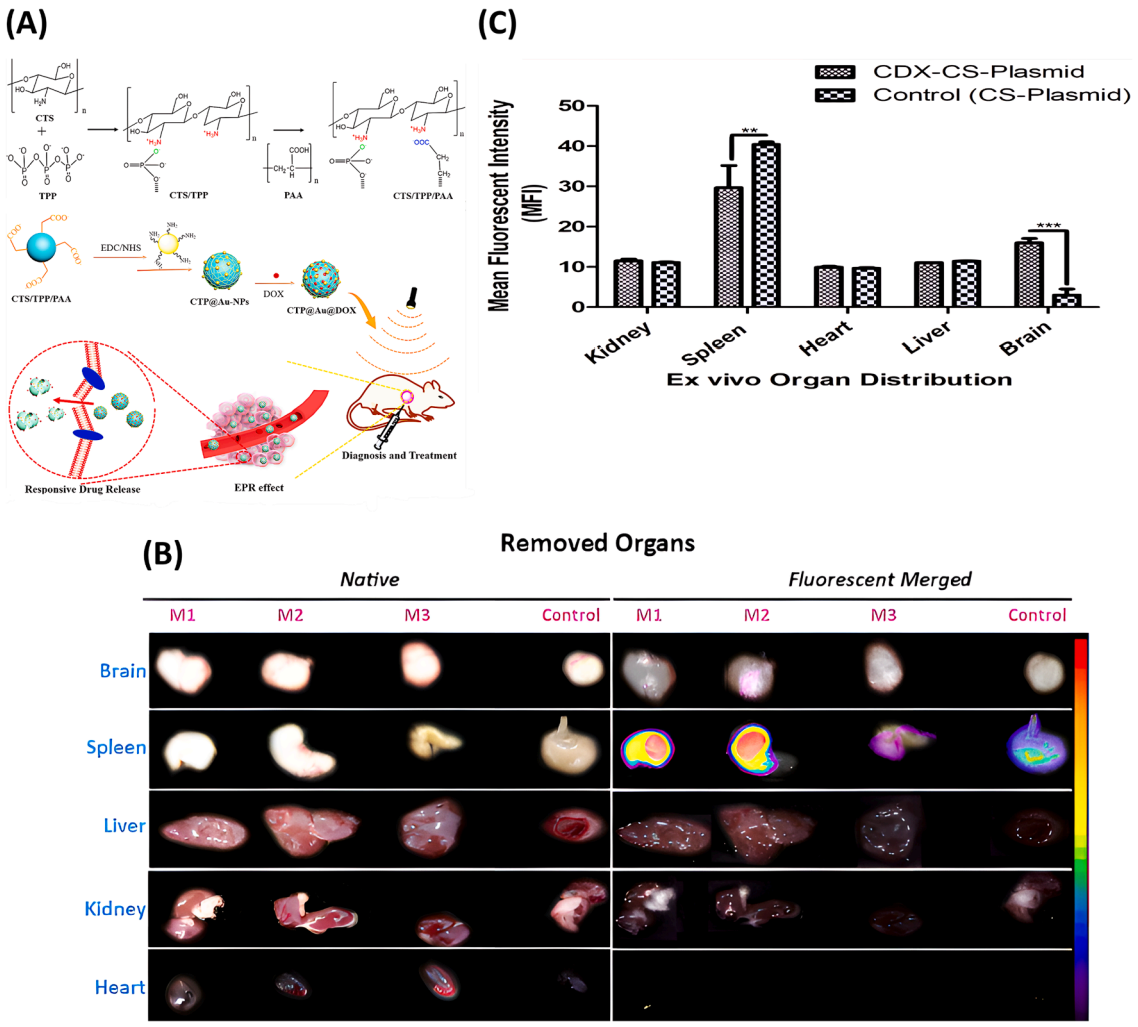


Fig. 10. Illustrates the creation process of CTS/TPP/PAA@AuNPs (CTPA) and its dual functionality as a theranostic agent. It serves as both a drug carrier for chemotherapy and a contrast agent for CT diagnostics. (b) Ex vivo images of mice were obtained using EtBr-labeled CS/pEGFP (control) and EtBr-labeled CS-PEG-CDX/pEGFP nanocomplexes. These images were captured 48 h after intraperitoneal injection of the NPs. The left side displays organ images, while the right side presents merged images with fluorescent labeling.(c) The fluorescence intensity of the brain and various organs was measured and analyzed, Reprinted with permission from Sepasi et al (2023) (Sepasi et al., 2023).

proteins and nucleic acids. Additionally, the design of nanogels with specific chemical structures (surface functionalization) allows for controlled and sustained drug release, enhancing therapeutic outcomes (Zhang et al., 2022; Sarmadi et al., 2024). In terms of surface functionalization peptides have enormous applications as potential ligands. Tian et al (Tian et al., 2012) synthesized TAT-PEG-GS NPs by modifying gelatin-siloxane nanogels with PEG and TAT peptide. These NPs demonstrated the ability to cross the BBB and accumulate in brain tissues, showing potential as nanoparticles systems for CNS delivery. Zhang et al (Zhang et al., 2022) presented a novel biomimetic nanogel system triggered by near-infrared irradiation to improve BBB penetration and enhance drug delivery into deep tumor regions. These nanogels, coated with erythrocyte membrane decorated with ApoE peptide, demonstrated significant suppression of tumor growth in orthotopic GBM models. Nanogels have shown significant potential in drug delivery to the brain due to their ability to bypass physiological barriers like the BBB (Zhang et al., 2022). These nanoscopic drug carriers exhibit remarkable capability to penetrate brain tissue effectively, making them highly promising for addressing various neurological illnesses encompassings neurodegenerative disorders, brain tumors, epilepsy, and ischemic stroke (Stawicki et al., 2021; Bazarbaeva et al., 2021). Several studies have investigated the application and nanogel in brain. In Table 11 some of them are listed.

Brachi et al (Brachi et al., 2020). suggests using polyurethane (PUR) NPs coated in a Poloxamer 407 thermosensitive hydrogel as a delivery system targeting GBM tumors (Fig. 13A). Administering drugs locally can be highly beneficial for treating brain illnesses, such as brain tumors, when NPs are able to bypass the BBB, which is a major hindrance to delivering drugs to the brain. The hydrogel formulation was adjusted, and it was confirmed that the time it takes for the gel to develop decreases as the concentration of poloxamer increases. A polymer concentration of 25 wt% was used in order to achieve a gelation period of 4 min at normal body temperature. The inclusion of NPs in the hydrogel demonstrated benefits by reducing the rate of cargo release and limiting sudden bursts of release. In order to evaluate the hydrogel's capacity to enhance the duration of NPs presence in the tumor, intracranial xenografts were created in immunocompromised mice. The NPs were infused with BODIPY fluorophore in order to enable the examination of their biodistribution in real-time Fig. 13B demonstrates the dispersion pattern of the model drug BODIPY in selected coronal sections near the injection site and along the sagittal axis in mice with tumors). The mice were administered hydrogels containing NPs at a dosage of 2.5 mg through intratumoral injection. A cohort of animals was administered NPs in liquid form, serving as a control group. The inclusion of NPs in the hydrogel extended the duration that NPs remained at the tumor site, preventing their movement away from the tumor and allowing them to

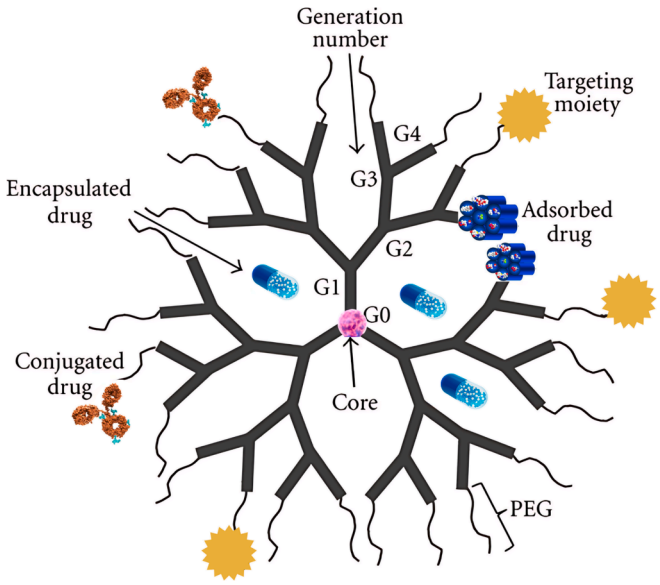


Fig. 11. Schematic Representation of Dendrimer Nanoparticles: A branched, tree-like structure with a core (G0) and successive generations (G1, G2, etc.).

cover a greater surface area of the tumor compared to NPs in a liquid suspension. The researchers reached the conclusion that these NPs show great potential as a method for delivering drugs to glioblastoma, allowing for increased drug concentration in the tumor while avoiding toxicity in the rest of the body.

4. Clinical translation

Significant advancements have been made in the field of nanomedicine in various areas including biology, chemistry, and engineering. Their ever-evolving potential for medical applications is filled with great promise. Despite its novelty, nanomedicine has attracted considerable interest and remains a prominent area of study and innovation. One area of particular interest is the use of nanotechnology in drug delivery and imaging for brain diseases. Researchers have made significant progress in developing functional NPs, with some already approved for use and others currently undergoing clinical trials and preclinical testing (Fig. 14). Also, some information about the findings of these trials is provided in Table 12.

The field of nano-based drug delivery has seen a remarkable surge in scientific publications, with the number of papers skyrocketing from less than 300 in 1999 to over 10,000 annually (Mu et al., 2018). These publications focus on studies that explore the improvement and expansion of nano-drug delivery systems. Throughout the last twenty years, there has been a consistent stream of 150 publications annually, showcasing clinical trials that have made remarkable advancements and breakthroughs (Mu et al., 2018). The number remains relatively stable in the present period, while research in non-clinical studies is experiencing significant growth. The slow progress in clinical research, in contrast to the rapid expansion of preclinical data, can be attributed to several challenges. These include the complexities of scaling up,

Table 8
Overview of various types of dendrimers.

Dendrimer Type	Core Structure	Surface Modifications	Applications	Ref
PAMAM Dendrimers	Well-defined spherical	Surface reconfigured with PEG	Drug and peptide delivery	(Igartúa et al., 2018; Shi et al., 2020)
PPI Dendrimers	Butylenediamine core	PEGylation and acetylation	Improving water solubility of drugs	(Noske et al., 2020; Patel et al., 2012)
PLL Dendrimers	Poly-l-lysine residues	Incorporating specific protein sequences	Gene transfection efficiency	(Gorzkiewicz et al., 2020; Janiszewska et al., 2016; Hegde et al., 2019)
Carbosilane Dendrimers	Carbon and silicon molecules	Modification to polar molecules	Drug Delivery	(Strašák et al., 2017; Chis et al., 2020)
Phosphorus Dendrimers	Cationic phosphorus core	Phosphorus termination and reactive end groups	Biological and theragnostic applications	(Posadas et al., 2022; Shcharbina et al., 2013)
Peptide Dendrimers	Branched polypeptide core	Branched polypeptide chains or non-peptide branching	Surfactants, drug and gene transporters	(Lalatsa et al., 2014; Cieślak et al., 2020)
Glycodendrimers	Carbohydrate moieties	Sugar residues on exterior surfaces or as central core	Site-specific delivery to lectin-rich tissues	(Zhang et al., 2022; Roy et al., 2013)
Polyglycerol Dendrimers	Glycerol core	Cationic amine end groups	siRNA delivery	(Sharma et al., 2020)
Citric Acid Dendrimers	Citric acid core	Modification with β-cyclodextrin or PEG	Drug delivery system	(Namazi et al., 2017; Taheripak et al., 2024)

Table 9
Summary of in vivo and in vitro studies Utilizing dendrimers.

Drug delivery	Nanoparticles	Application	model	Results	Ref
	Folic acid (FA)-decorated polyamidoamine (PAMAM) dendrimer G4 (G4-FA)	Gene therapy	In vitro	G4-FA competes with free FA for folate receptor (FR) binding, enhancing DNA plasmid uptake and gene expression in FR-rich cells.	(Xu et al., 2016)
	doxorubicin + folic acid conjugated PAMAM modified with borneol	Chemotherapy	In vivo	Enhanced doxorubicin accumulation in brain tumors results in enhanced suppression of tumor development and a longer median survival time.	(Xu et al., 2016)
	dendrimer–rapamycin conjugate (D-Rapa)	Chemotherapy	In vivo	Decreased tumor size, specifically aimed at tumor-associated macrophages (TAMs), mitigated rapamycin-induced kidney damage.	(Sharma et al., 2020)
Imaging	Amine-terminated amphiphilic dendrimer	PET imaging of tumors	In vivo	• Capable of identifying low-glucose-uptake tumors that are challenging to detect with conventional imaging methods. • Exhibits a promising safety profile and pharmacokinetics characteristics.	(Garrigue et al., 2018)
Combination Therapy	tLyp-1-conjugated PAMAM dendrimer	BBB-targeting	In vivo	• Associated with increased levels of CD54+/CD69 + natural killer (NK) cells and CD4+/CD8 + T cells within malignancies • Extended lifespan of mice with gliomas	(Jin et al., 2021)

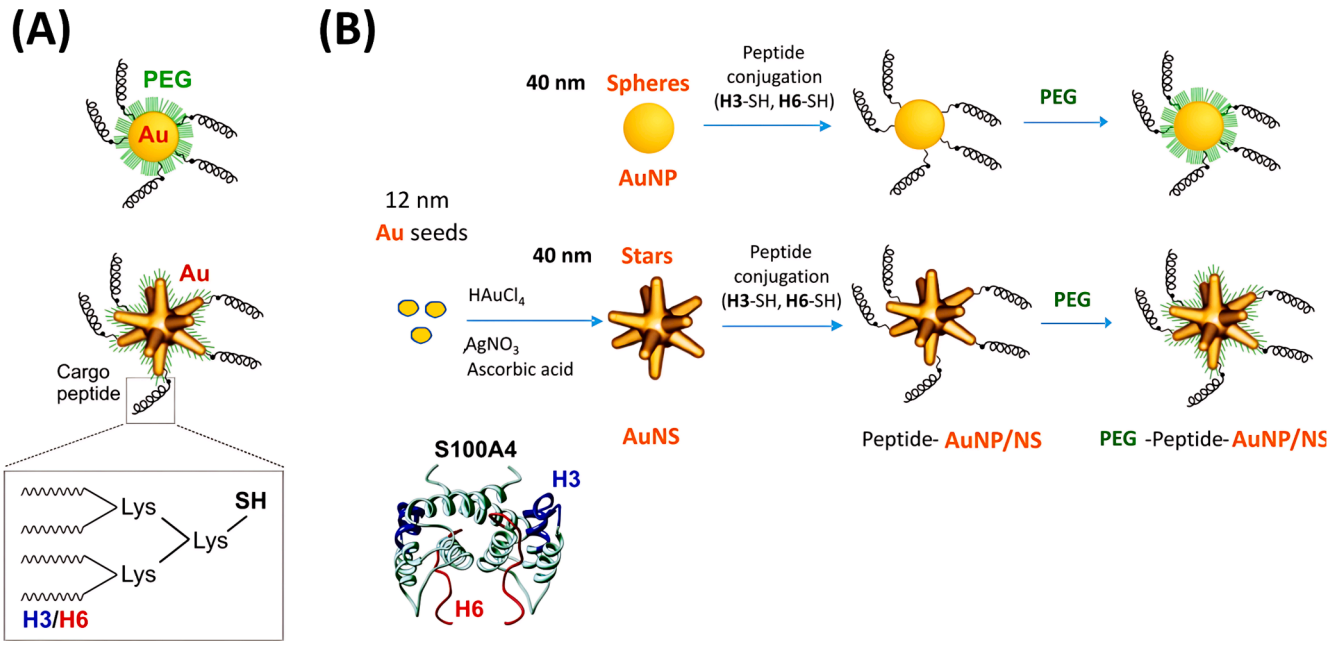


Fig. 12. The creation of gold nanoparticles conjugated with (+/–PEG) and cargo peptides (H3/H6) is depicted in (a). These peptides are formed as tetramers, with four monomers connected to a lysine backbone. The thiol group used for conjugation to gold (−SH) is located on the lysine backbone and does not interfere with the neuroactive motifs. The location of the H3 and H6 motifs in the 3D structure of the parent protein (S100A4) is also illustrated. (b) shows a summary of the fabrication process and the structures created at each step of the protocol to build (±PEG)–H3/H6-AuNP/AuNS. The schematic illustration in (a) and the scheme in (b) provide a detailed overview of the synthesis process and the structures obtained at each step, Reprinted with permission from Morfill et al (2022) (Morfill et al., 2022).

Table 10
Synthesis methods of nanogels.

Method		Description	Ref
Chemical method	Chemical Crosslinking	This technique forms covalent bonds between polymer chains using crosslinking agents (e.g., glutaraldehyde, genipin) or radical polymerization.	(Mashabela et al., 2022)
	Emulsion Polymerization	Emulsion polymerization uses water-based monomer polymerization with surfactants and initiators, producing evenly dispersed nanogels.	(Lovell and Schork, 2020)
	Radical Polymerization	Radical polymerization initiates polymerization via free radicals that react with monomers to form polymer chains, commonly used for hydrogel production.	(Matyjaszewski and Tsarevsky, 2014)
Physical method	Physical Crosslinking	Nanogels can be synthesized via hydrogen bonding, electrostatic, or host–guest interactions without chemical crosslinkers.	(Haraguchi et al., 2011)
	Self-Assembly	Nanogels form through self-organization of amphiphilic block copolymers or surfactants via hydrophobic interactions, resulting in hydrogel-like nanostructures.	(Patel et al., 2023)

ensuring stability, and effectively managing material costs. Unfortunately, the publication of clinical study findings can be a time-consuming process, leading to a limited number of NPs currently being tested and approved by regulatory agencies. However, many clinical trials also show unpredictable results that do not meet their intended goal. He et al. (He et al., 2019) conducted a recent investigation into the efficacy of NPs in oncology treatment across different clinical trial phases. Their findings unveiled varying success rates: 94 % in phase I, 48 % in phase II, and a stark decrease to 14 % in phase III. Additionally, their analysis estimated a mere 6 % likelihood of transitioning from phase I to clinical approval.

4.1. Challenges

Despite promising results in preclinical studies, many formulations of NPs fail to meet expectations in clinical trials. There are certain challenges that may arise when using NPs in clinical applications. These challenges can be linked to insufficient preclinical research, resulting in problems like limited effectiveness and potential toxicity. Additionally, unexpected hurdles in the market, such as high costs and intricate production processes, can also pose obstacles. Next, we will delve deeper into the factors contributing to the limited effectiveness of NPs in clinical settings.

Preclinical Models: Creating efficient drug delivery systems for the brain presents considerable obstacles, largely stemming from the intricate nature of both pre-clinical and clinical models. In vitro models of the BBB frequently utilize human brain endothelial cell lines such as hCMEC D3 and bEND.3, or primary brain endothelial cells sourced from animals. These cells are generally grown in transwell or microfluidic systems utilizing semi-permeable membranes. Co-culturing endothelial cells alongside other cell types, including pericytes and astrocytes, improves barrier properties by elevating tight junction (TJ) and transporter expression, thereby creating a more authentic environment for investigating BBB function (Jackson et al., 2019; Bhalerao et al., 2020; Canfield et al., 2017). Nonetheless, the inconsistencies in cultural conditions and the absence of physiological relevance to human scenarios continue to pose significant challenges. In a similar vein, in vivo models primarily utilize rodents that have been implanted with human xenografts or rodent glioblastoma cell lines. While commonly employed, these models exhibit notable differences between the BBB characteristics in humans and rodents. Analytical techniques such as measuring drug concentrations in brain homogenates tend to be invasive and constrained, frequently necessitating a significant number of animals while yielding only single-sample data. Methods such as microdialysis and clinical

Table 11
Summary of in vivo and in vitro studies Utilizing nanogel.

Nanogel System	Application	Model	Result	Ref
Carboxymethyl cellulose-grafted poly (N-isopropylacrylamide-co-methacrylic acid) + gadopentetic acid/branched polyethylenimine	Theranostics	in vivo	MRI traceable, rapidly gelating hydrogels loaded with epirubicin and paclitaxel showed significant tumor growth inhibition in vivo	(Wang and Wu, 2017)
Pectin-based hydrogel + poly (ethylene glycol)-block-polylactic acid micelles carrying etoposide and olaparib	Brain Tumor	in vivo	Rapid release of drugs, bioadhesive hydrogel adheres to brain tissues, no neurotoxicity observed in mice	(McCrorie et al., 2020)
Poly (N-vinyl pyrrolidone)–co-acrylic acid nanogels + insulin	Nose-to-brain delivery	In vivo and in vitro	Increased insulin levels in brain regions after intranasal administration, mucoadhesive properties enhance retention and penetration, resistance to proteolytic enzymes	(Picone et al., 2018)
Disulfide crosslinked polyglycerol-scaffold nanogels	glioblastoma therapy	In vivo and in vitro	Facilitated cellular uptake, endosomal escape, and intracellular release of microRNA in GBM cells, significant tumor growth inhibition in vivo	(Shatsberg et al., 2016)
Chitosan and polyanionic pentasodium triphosphate nanogels + methotrexate	drug delivery	In vivo and in vitro	Improved drug delivery to the brain, a significant increase in drug plasma and brain concentrations, "Trojan Horse" effect	(Azadi et al., 2013)
pH/temperature-sensitive poly (N-isopropylacrylamide-co-acrylic acid) nanogels + citric acid + Fe3O4 nanoparticles	Imaging	In vivo	A multifunctional contrast agent for MRI and optical imaging of gliomas shows tumor-specific accumulation, biocompatibility, and no detectable toxicity.	(Jiang et al., 2013)

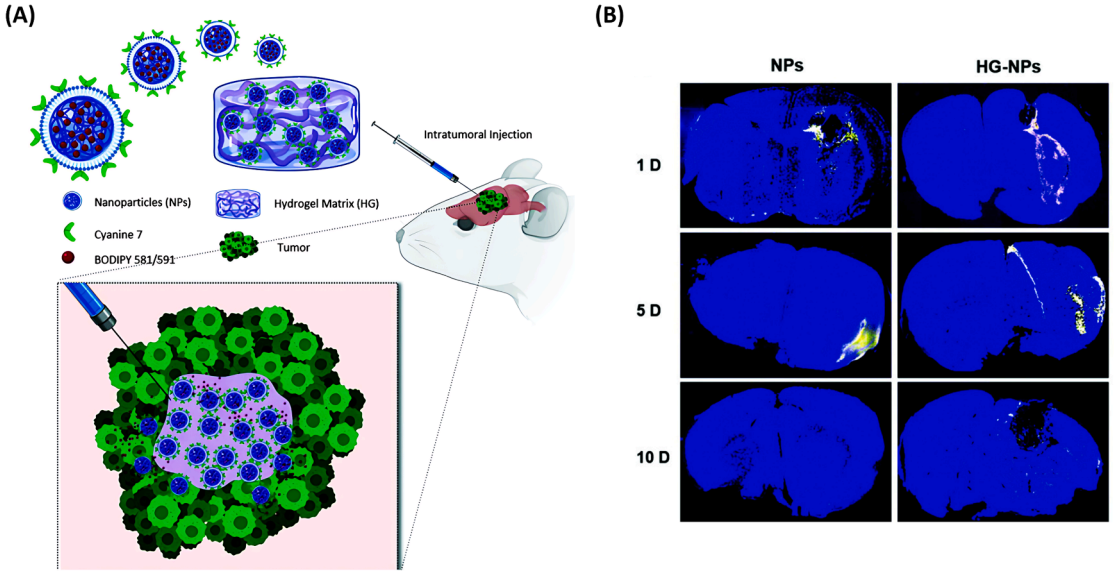


Fig. 13. (a). schematic illustrating the HG-NPs method used for delivering substances directly into tumors. The solution of HG-NPs is administered intratumorally at ambient temperature. The HG component undergoes quick solidification upon administration as a result of the temperature rise. The outcome is a high-gradient depot that captures NPs, increasing their local retention and reducing their movement away from the tumor mass. (b). Representative confocal pictures of coronal brain sections at the injection site from animals with tumors that were injected with NPs and high-grade NPs (HG-NPs). The nuclei were labeled with DAPI, resulting in a blue tint. The yellow color represents the presence of BODIPY, Reprinted with permission from Brachi et al (2022) (Brachi et al., 2020).

imaging techniques (e.g., MRI, PET, and CT) provide less invasive options, yet they continue to pose challenges for routine application in studies (Dai et al., 2018; Birngruber and Sinner, 2016; Kashkooli et al., 2021). The toxicity of nanoparticles and their compatibility with biological systems are critical factors in the delivery of drugs to the brain. Inorganic nanoparticles are known to exhibit toxic effects, including the production of reactive oxygen species (ROS) and the disruption of cellular membranes (Soares et al., 2018; Hu and Hammarlund-Udenaes, 2020; Kashkooli et al., 2020). Organic nanoparticles are often viewed as safer alternatives because they are made from naturally occurring elements such as carbon and hydrogen; however, they still present certain risks. Aspects like dimensions, morphology, solubility, and aggregation are crucial in determining their toxicity. Organic nanoparticles have the potential to accumulate in multiple organs such as the spleen, liver, kidneys, and brain, which could lead to systemic and neurotoxic effects. Within the brain, interactions occur with neurons, astrocytes, and microglia, resulting in inflammation and cytotoxic effects (Masserini, 2013; Zottel et al., 2019; Teleanu et al., 2018; Fan et al., 2021). Lipid-based nanoparticles are frequently regarded as safer options because of their GRAS (generally recognized as safe) ingredients and extensive clinical history. Nonetheless, the byproducts of their degradation, including free fatty acids and phospholipids, have the potential to trigger oxidative stress, inflammation, and neuronal injury. The selection of surfactants and lipid components in Lipid-based nanoparticle formulations significantly influences their biodegradation rates and safety (Hu and Gao, 2010; Costa et al., 2016; Blasi et al., 2007). Polymeric nanoparticles and dendrimers pose further complexities. Polymeric nanoparticles, such as those derived from poly(lactic-co-glycolic acid) (PLGA), generate acidic by-products upon degradation, potentially worsening pre-existing brain inflammation. The stability of these nanoparticles and their potential for accumulation present significant concerns regarding long-term safety (Zhang and Zhang, 2017; Anajafi and Mallik, 2015; Pawar et al., 2013). Dendrimers hold significant potential because of their precisely controlled structures; however, they encounter challenges including hemolytic toxicity, unpredictable drug release, and limitations in systemic clearance. Smaller dendrimers

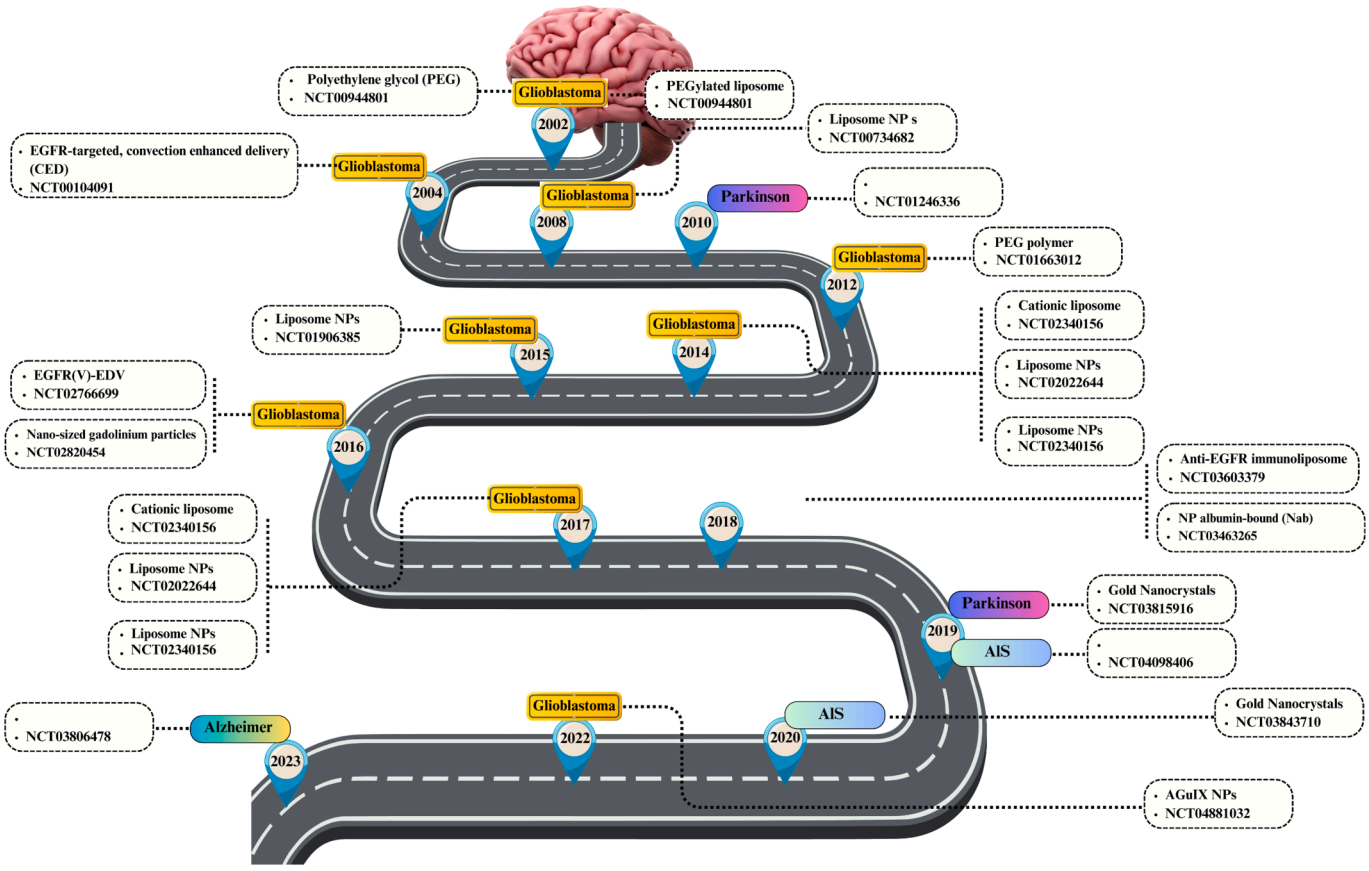


Fig. 14. Timeline of Approved Nanoparticles for Therapeutics and Diagnostics: Key developments over two decades, targeting diseases like glioblastoma, Parkinson's, Alzheimer's, and AIS, with references to clinical trials (NCT numbers).

Table 12
Summary of Clinical Trials on Nanoparticle Therapeutics: Key formulations, targets, outcomes, and findings for various cancers.

Trial Code	Nanoparticles	Administration Route/ Targeting Mode	Clinical Goal	Findings/Outcomes	Refs
NCT00944801	PEGylated liposomal doxorubicin (PEG-Dox)	Intravenous; The BBB penetration enhancement	Evaluate efficacy and tolerability of PEG-Dox and prolonged temozolomide administration alongside radiotherapy in newly diagnosed glioblastoma patients.	The combination therapy was tolerable with minor toxicity, achieving a PFS-12 of 30.2 % and a median overall survival of 17.6 months, similar to standard treatments.	(Beier et al., 2009)
NCT01663012	Etirinotecan Pegol (NKTR-102): A next-generation PEGylated topoisomerase inhibitor.	Intravenous infusion, targeting tumor cells through prolonged systemic exposure and enhanced permeability.	Evaluate progression-free survival (PFS), overall survival (OS), safety profile, and imaging response rates in bevacizumab-resistant high-grade gliomas.	6-week PFS: 55 %; Median PFS: 2.2 months; Median OS: 4.5 months. Imaging response (partial response) in 16.7 % of glioblastoma patients. Favorable safety profile with manageable toxicities such as mild diarrhea and fatigue.	(Nagpal et al., 2015)
NCT01906385	Rhenium (186Re) Obisbemeda (Rhenium Nanoliposome, 186RNL)	Intraventricular catheter via Ommaya reservoir	Evaluate safety, tolerability, and feasibility in treating leptomeningeal metastases (LM)	Phase 1 trial of 186RNL showed good tolerability, mild adverse events, high CNS radiation absorption, reduced tumor cells in cerebrospinal fluid, and improved LM symptoms. Dose escalation is ongoing.	(Brenner et al., 2023)
NCT02340156	SGT-94 Tumor-targeted liposomal nanodelivery system carrying RB94 gene	Intravenous; targets transferrin receptor (TfR) on tumor cells	Assess safety, tolerability, and preliminary efficacy in metastatic genitourinary cancers	SGT-94 was well-tolerated with no dose-limiting toxicities. Clinical activity included stable disease, partial responses, and one complete remission of lung metastasis, with tumor-specific delivery confirmed.	(Siefker-Radtke et al., 2016)

undergo renal filtration for clearance, whereas larger dendrimers are more susceptible to recognition and elimination by the immune system. Furthermore, numerous dendrimers produce acidic by-products that may trigger localized inflammation, underscoring the necessity for investigations into safe, biodegradable dendrimer designs (Zhu et al., 2019; Souri et al., 2022). To address these challenges, it is crucial to develop more physiologically relevant blood–brain barrier models and implement advanced analytical techniques. Enhancing in vitro and in

vivo models to more accurately reflect human blood–brain barrier properties and incorporating non-invasive imaging techniques like MRI and PET may advance the assessment of drug delivery systems (Olbrich et al., 2002). Moreover, thorough investigations into the neurotoxic effects of ONPs, taking into account aspects such as composition, size, and surface modifications, are crucial. The advancement of safer polymeric nanoparticles and dendrimers, aimed at reducing toxic by-products and promoting efficient clearance, continues to be a vital focus for investigation (Saraiva et al., 2016; Tang et al., 2019). By tackling these deficiencies, drug delivery systems can enhance their safety and efficacy, paving the way for their integration into clinical practice.

Commercialization: Ensuring the clinical translation of NP synthesis requires a focus on large-scale and reproducible production. However, this can be quite challenging for numerous NPs, resulting in their failure to reach the market. Managing and fine-tuning small quantities is relatively straightforward, but when it comes to producing on a larger scale and ensuring top-notch quality, the costs and difficulties increase significantly. Not only are manufacturing costs a concern, but the expenses associated with preclinical development and conducting clinical trials can be exorbitant. Obtaining regulatory approval for new nanotherapeutics can be quite challenging, particularly when there are already similar products available in the market with the same target indication. However, the global expansion of nanomedicine commercialization continues. Currently, the nanomedicine market is primarily dominated by North America and Europe. These regions have taken the lead in early nanomedicine development and have established regulatory frameworks. The industry in Asia is experiencing significant growth, thanks to a surge in funding for nanomedicine research and a growing fascination with nano-based therapies (Zhang et al., 2020). Given the challenges associated with bringing nanomedicine to market, it's understandable that investors may approach this field with caution. Furthermore, the considerable expenses associated with the development of nanomedicines present additional obstacles during the preclinical and clinical phases of nanomedicine advancement. In addition, given the constraints of preclinical validation, it is frequently essential to carry out numerous clinical trials and allocate additional resources to enhance a formulation. For small biotechnology companies and academic laboratories, the cost of developing a potential nanomedicine for clinical use can pose a significant challenge. Even for large pharmaceutical companies, these expenses can present a considerable challenge when it comes to investment. The Tufts Center for Study of Drug Development estimates that the development of a new nanotherapy comes with a hefty price tag of around $2.558 billion (Zhao et al., 2024). Usually, a biopharma startup company, unlike your average computer tech startup, requires a consistent flow of funding over multiple years to advance its product from the initial discovery phase to clinical trials and ultimately obtain regulatory approval. The clinical trial stage is a critical and costly phase, where even a single failure can have devastating financial consequences. This holds especially true for cancer nanomedicines, which frequently encounter the threat of termination throughout their development and testing phases (Moore et al., 2018). Despite securing funding and receiving approval, the cost of nanomedicine tends to be higher compared to conventional chemotherapy drugs. This is due to the significant expenses incurred during their development. Regrettably, the increased expense frequently results in minimal advantages for the patient, offering only a brief extension of survival or a temporary slowdown in the disease's progression. These cost/benefit considerations pose a significant obstacle to the widespread acceptance of nanomedicine and are a cause for concern among potential investors. Financial challenges can pose significant obstacles for startup companies focused on the development of nanomedicine. As an illustration, BIND Therapeutics was established in 2007 with the aim of advancing the Accurins® platform. The company secured an impressive $877.7 million through various channels, including capital markets, partnerships with major pharmaceutical companies, and investments from venture capital firms (Hao et al., 2023). A Phase II study that did not yield the desired results resulted in a significant decline in stock prices (Huang et al., 2022; Souri et al., 2022), ultimately leading to the acquisition of the company by Pfizer for $40 M (Souri et al., 2022). On the other hand, developing an effective nanotherapy can be a magnet for investment. For instance, Celator Pharmaceuticals secured approximately $170 million in venture capital funding, resulting in the successful approval of Vyxeos (Lancet et al., 2018). While it may be premature to assess the commercial triumph of Vyxeos, it managed to generate a substantial $75 million in its inaugural year of launch in 2018 (A.t.m.t.r.m.b., 2024).

5. Future outlook and concluding remarks

The BBB is essential for maintaining the optimal operation of the CNS. Any disturbances to this barrier can have significant implications for the progression of various brain disorders. Gaining a deeper understanding of how the brain is regulated in both healthy and diseased states is crucial for advancing our knowledge of disease pathophysiology. The exact cause of BBB dysfunction is still not fully understood. It could be due to the loss of signals that maintain the CNS or the presence of signals that lead to a breakdown in a pathological state. However, we have gained extensive knowledge about the physical and molecular changes that occur beyond the breakdown of the BBB in various diseases. By utilizing the current knowledge of BBB dysfunction, which is associated with the heightened presence of specific receptors in the cells lining the brain's blood vessels, such as RAGE in AD or lactoferrin in Parkinson's disease, it is feasible to create a more effective method for administering medications to the injured brain. Small agents can be used to enclose drugs, offering protection and prolonging their circulation time. These agents also allow for a controlled release of the drugs at the specific site of the lesion after being injected intravenously. Recent advancements have identified certain principles that can improve the transportation of NP formulations across the BBB. For instance, researchers have extensively examined the utilization of specific ligands on the surface of NPs, as well as factors like ligand density and NP shape, over the last ten years. Moreover, the recent advancements in antibody transport across the BBB could serve as a source of inspiration for NP bioengineers to develop novel formulations with improved characteristics. In recent years, more and more research has been conducted on the potential benefits of NPs in treating neurological disorders in animal models. These disorders include stroke, AD, and Parkinson's disease. Additional research is needed to better understand the variations in NP transport in animal models with and without diseases. It is important to acknowledge the limitations of experimental models, as they cannot completely replicate specific human diseases. Although it is widely recognized that the properties of the BBB undergo significant changes in models of Parkinson's disease, Alzheimer's disease, or stroke, there is a lack of comprehensive studies examining the influence of NP physicochemical properties on NP transport and distribution in the brain.

Opportunities for the delivery of drugs and other therapeutic substances to the brain are greatly enhanced by ONPs. As an example of a biocompatible nanoparticles, ONPs not only provide a carrier system that can fix many drug pharmacokinetic issues (such as poor solubility and permeability), but they also have superior properties compared to inorganic counterparts in order to mimic the physicochemical conditions found in the biological environment. Furthermore, ONPs may accomplish optimal BBB penetration and brain accumulation due to their stealth, targeting, and triggering methods. Consequently, the remarkable increase in research and new applications has clearly shown the advantages of ONPs in brain drug delivery and other therapeutic agent administration. This review has attempted to include a broad spectrum of these uses, despite the fact that the majority of the progress and innovations in ONP-based therapy have been focused on the treatment of glioma. Since most investigations are now limited to preclinical studies, further research is needed to enhance the pharmacokinetic and

toxicological features of ONPs in order to conduct clinical trials and advance their development as a viable treatment option for AD, PD, and cerebral ischemia/reperfusion (CIR).

Insufficient clinical trials and limited academic-to-clinical translation are attributed to the several obstacles that the development of ONPs currently encounters. An essential problem is in the complexity of completely characterizing the many structural and dynamic processes that take place when ONPs interact with biological surfaces. Therefore, it is necessary to include a methodical investigation of the impact of crucial factors, such as surface density, chemistry, NP size, and topology, into the development process. Most of the time, these important aspects of ONP design are not well characterized, and as a result, NPs are made and evaluated in vivo in animal models without a complete knowledge of why they have unexpected biological interactions and accumulate off-target. The creation of ONPs that can target particular brain cells, such as dopaminergic neurons (PD targets), microglia (neuroinflammation targets), or neural stem cells (neuronal repair targets), is a significant problem related to this off-target dispersion and deserves additional attention. Determining the neurotoxicity, clearance mechanism, and long-term negative effects of ONPs takes time, which is another restriction. It could take decades for people to undergo a complete evaluation of ONP toxicity. The scalability and repeatability of ONP manufacturing methods are additional important considerations since they are real-world issues that might impede their clinical translation if not resolved.

These NPs have a high BBB-crossing capability, which gained considerable attention in the medical field. Still, these NPs must pass scientific and regulatory tests before being used for clinical brain delivery. So, it is expected that the ONPs created in the preclinical experiments detailed here will soon be available to enhance the lives of patients suffering from neurological disorders.

CRediT authorship contribution statement

Zahra Sadat Razavi: Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Seyed Sina Alizadeh:** Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Fateme Sadat Razavi:** Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Conceptualization. **Mohammad Souri:** Writing – review & editing, Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Conceptualization. **M. Soltani:** Writing – review & editing, Validation, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing 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.

Data availability

No data was used for the research described in the article.

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