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Advancements in Using Polymeric Nanoparticles for Blood−Brain Barrier Penetration in Neurological Disorders

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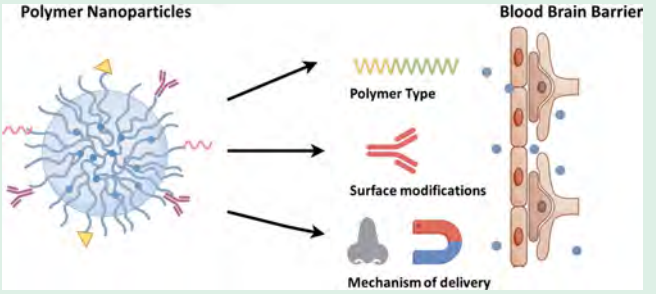
ABSTRACT: Neurological disorders and glioblastoma represent a significant global health burden, affecting billions of individuals and contributing to high rates of morbidity and mortality. A primary obstacle in treating these conditions is the presence of the blood−brain barrier (BBB), a protective barrier that restricts the entry of most therapeutic agents into the brain. Despite this challenge, advancements in nanotechnology, specifically the development of polymeric nanoparticles, offer promising solutions for overcoming the BBB. Key strategies include surface modifications like PEGylation to enhance circulation time, receptor-mediated targeting for specific brain cells, and stimuli-responsive nanoparticles that release drugs in response to pH or reactive oxygen species. Ultrasound-guided delivery, intranasal administration, and magnetic nanoparticle guidance further enhance targeted delivery, while multifunctional nanoparticles enable combination therapies. These nanoparticles, with their customizable properties, allow for targeted and sustained delivery of drugs to the central nervous system, providing new hope in the treatment of both neurodegenerative diseases and brain cancers. In this review, we explore recent strategies that exploit polymeric nanoparticles to improve drug delivery across the BBB, highlighting their potential in revolutionizing therapeutic approaches for neurological disorders.



KEYWORDS: *blood−brain barrier, polymeric nanoparticles, nanotechnology, stimuli-responsive, cancer, neurological disorders, targeted delivery*

1. INTRODUCTION

Neurological disorders affecting the brain and spinal cord are leading contributors to global morbidity and disability, with stroke ranking as the second most common cause of death. These disorders encompass a range of conditions, including Parkinson's disease, Alzheimer's disease (AD), Huntington's disease, motor neuron disease, multiple sclerosis, traumatic brain injury, stroke, and brain cancers.[1] Based on the World Health Organization,[2] over 1 in 3 people are affected by neurological conditions, and in 2021, more than 3 billion people worldwide were living with a neurological condition. As the global population ages and grows, there is an increasing need for more effective management and treatment strategies for neurological diseases.[3]

Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, are marked by the gradual loss of neuronal function.[4] Key pathological features that drive the progression of these diseases include protein aggregation (such as amyloid-β, τ, and α-synuclein), oxidative stress, and mitochondrial dysfunction, which ultimately lead to neuronal death. These conditions are strongly associated with aging, oxidative damage, and genetic and environmental factors.[5,6] Among these factors, mitochondrial dysfunction is pivotal in neurodegeneration, largely due to its role in generating reactive oxygen species (ROS), which, in turn, exacerbate oxidative damage.[7,8] The interaction between protein aggregation and mitochondrial dysfunction is critical in the progression of these diseases, with protein aggregates further impairing mitochondrial function and intensifying oxidative stress.[9]

Glioblastoma (GBM) is an aggressively malignant primary brain tumor characterized by limited treatment options and a poor prognosis.[10] Current treatment modalities, which include surgical resection, radiation therapy, and chemotherapy with Temozolomide (TMZ), have not significantly improved outcomes due to GBM's invasive inherent characteristics, challenges with drug delivery beyond the blood−brain barrier (BBB), and resistance to standard therapies. Moreover, the antitumor efficacy of TMZ is substantially hampered by its limited ability to cross the BBB (reaching only 20% of blood

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concentration) and various cellular mechanisms conferring therapeutic resistance.[11] A major challenge in treating GBM is the effective elimination of infiltrating cancer cells that persist in the brain tissue even after the primary tumor has been surgically removed. These residual cancer cells lead to tumor recurrence and metastasis.[12]

A major hurdle in the treatment of brain cancer and neurodegenerative diseases is the BBB, which limits the delivery of therapeutic agents to the brain. Nanotechnology holds great promise for treating neurological disorders, particularly in overcoming the BBB to deliver drugs to targeted cells. Polymeric nanoparticles (NPs) are especially promising for targeting the central nervous system (CNS) due to their adjustable size (10−1000 nm), nontoxicity, biocompatibility, and controlled drug release. They can be modified with specific ligands to target receptors on endothelial or cancer cells, enhancing their ability to cross the BBB. These nanoparticles also have longer circulation times and can be biodegradable. Once inside the cells, the polymeric matrix can be triggered to release the drug, leading to a targeted and sustained therapeutic effect. Additionally, polymeric nanoparticles can deliver a wide variety of drugs through hydrophilic, hydrophobic, or electrostatic interactions, as well as responsive covalent bonds

In previous reviews, advancements in polymeric nanoparticles for crossing the BBB in treating neurological disorders have highlighted significant progress and ongoing challenges. Studies such as those by Zhang et al. (2021) have emphasized the tunability of these nanoparticles, with a focus on surface modifications, particle size, and shape to enhance BBB penetration, and noted the necessity for improved preclinical models like BBB-on-a-chip for more accurate testing.[13] Nance et al. (2014) demonstrated the potential of using MRI-guided focused ultrasound (FUS) for targeted, noninvasive BBB disruption combined with polymeric nanoparticle delivery to improve brain drug distribution.[14] Additionally, Khan et al. (2018) reviewed the varied nanoparticle types, including polymeric systems, which exploit receptor-mediated mechanisms for improved CNS delivery.[15]

Our review distinguishes by integrating newer multifaceted strategies (Table 1). In this review, we highlight the current strategies in the exploitation of polymeric nanoparticles as a drug delivery vehicle in crossing the BBB to treat various neurological disorders. This review provides a summary of the major types of polymeric NPs used in neurological disorders and GBM in the past 6 years (from 2019 to 2024), the ways in which these NPs can be modified and delivered in order to bypass the BBB, and strategies for specific targeting of NPs to cancer and brain endothelial cells.

2. NAVIGATING THE BBB: CHALLENGES

The BBB is a complex structural, functional, and physiological barrier that precisely controls the movement of nutrients, ions and cells between the brain and systemic circulation. The BBB comprises of pericytes, astrocytes, cerebral endothelial cells and the basement membrane. Together with neurons and glial cells, these components form the neurovascular unit, which is essential for brain function[16]

Glial cells play a critical role in the CNS. Pericytes are smooth muscle cells that extend across several endothelial cell lengths, form an irregular layer, and help to regulate endothelial cell activity. They also act as macrophages during inflammation, providing a secondary line of defense after the endothelial tight junctions. Astrocytes, with their star-shaped morphology, are vital for maintaining BBB integrity. They secrete soluble factors like β-2 microglobulin and transforming growth factor β, which enhance the expression of tight junction proteins on endothelial cells. An intact BBB restricts the entry of more than 98% of small molecule drugs specifically those with a molecular weight greater than 400 Da and nearly 100% of large molecule drugs.[17]

Cerebral endothelial cells are characterized by their nonfenestrated nature and extensive mitochondria, forming tight junctions that meticulously control molecular transport across the endothelium.[18] The interendothelial space features transmembrane protein complexes, including occludin, claudin, and junctional adhesion molecules.[19] These tight junction proteins engage in homophilic interactions to create a highly selective barrier exclusive to the cerebral endothelial cells.[20] The apical side of the endothelial cells faces the blood flow within the brain capillaries, while the basolateral side interfaces with the cerebrospinal fluid and is supported by a basement membrane approximately 30−40 nm thick.[21] This membrane is composed of collagen type IV, laminin, heparan sulfate proteoglycans, fibronectin, and other extracellular matrix proteins.

Neurological disorders resulting from brain cancer, neuroinflammation and traumatic brain can compromise BBB's structural integrity and function. In brain cancers, this barrier is often termed as blood−brain tumor barrier (BBTB), which exhibits considerable heterogeneity, including variable permeability and active efflux of molecules. GBM and neurodegenerative disorders disrupts the BBB through various anatomical and physiological mechanisms.[22] The downregulation of tight junction proteins, such as claudin and occludin, coupled with the upregulation of BBB transporter proteins, leads to increased BBB permeability. Additionally, GBM co-opts the local vasculature to form new blood vessels, which further compromises the barrier and enhances vascular leakiness.[23] Efflux pumps, which have long posed challenges in drug development, are markedly upregulated in GBM, obstructing the entry of potentially therapeutic agents into the tumor. Consequently, these mechanisms create a paradox where increased BBB permeability allows tumor-promoting substances to penetrate the tumor bed, while simultaneously restricting the access of antitumorigenic drugs.[24] However, in many low-grade brain tumors and their peripheries, the BBTB closely resembles the BBB. Aging also contributes to barrier dysfunction due to changes in endothelial cell phenotypes and reduced tight junction integrity. Additionally, the BBB can be temporarily disrupted using methods such as FUS with microbubbles, focused radiation therapy, or chemical modifications with hypertonic solutions like mannitol.[25]

Neurological disorders such as Alzheimer's and multiple sclerosis share several mechanisms of BBB disruption similar to those seen in brain cancers like GBM. These include the downregulation of tight junction proteins like claudin and occludin, which increase BBB permeability,[26] and the upregulation of efflux transporters such as P-glycoprotein, which restricts therapeutic drug entry.[27] Additionally, neuroinflammatory conditions and oxidative stress activate matrix metalloproteinases (MMPs), leading to the degradation of the BBB's structural integrity, exacerbating the permeability issues. These mechanisms create significant challenges in treating both neurodegenerative disorders and brain tumors effectively.[28]

Therefore, crossing the BBB presents significant challenges for drug delivery due to its complex structure and function described above. The BBB is composed of tightly packed endothelial cells that form tight junctions, preventing most

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Table 1. Combination of Various Polymeric NP Strategies in the Treatment of Various Neurological Disorders in the Past 5 Years

nanosystem	size	shape	ζ potential	strategies	important findings	disease model	refs
Docetaxel-loaded chitosan NPs	187−306 nm	roughly spherical particles	N/A	•chitosan-functionalized •PEGylation •transferring receptor targeting	A synergistic effect was noted when chitosan and transferrin were combined in nanoparticles. Chitosan contributed bioadhesivity, while transferrin facilitated receptor-mediated endocytosis.	in vitro C6 glioma cells	38
R-flurbiprofen- and paclitaxel-loaded PLGA NPs	144−187 nm	spherical particles	+31.4 to +47.8 mV	•chitosan-functionalized PLGA NPs •PEGylation	Combination therapy using paclitaxel and *R*-flurbiprofen nanoparticles showed increased antitumor activity against glioma and reduced inflammation in the surrounding area.	rat RG2 orthotopic glioma tumor model	39
N,*N*,*N*-trimethylchitosan (TMC) and thermosensitive PF127 NPs for the delivery of docetaxel	50−200 nm	spherical particles	N/A	•chitosan-functionalized	The DTX-loaded hydrogel system significantly inhibits the growth of orthotopic GBM xenograft tumors compared to the control. These results indicate that the PF127-TMC/DTX hydrogel system could be a promising candidate for delivering anticancer chemotherapy to brain tumors.	mice orthotopic U87MG model	40
morusin-loaded PLGA NPs	173−242 nm	spherical particles	−10.51 to −20.1 mV	•PLGA NPs •chlorotoxin as a targeting moiety for chloride channels expressed in glioma tumor cells, as well as for MMP	Antiproliferative, apoptosis, and other cell-based assays showed that NPs significantly inhibited U87 and GI-1 glioma cells. Key indicators of cytotoxicity, such as increased ROS generation, enhanced caspase activity, cytoskeletal destabilization, and reduced MMP activity, were observed in GBM cells treated with NPs.	in vitro U87 and GI-1 glioma cells	41
chitosan-coated PLGA NPs loaded with carmustine	232 nm	spherical particles	+30.8 mV	•chitosan-functionalized •PLGA NPs •intranasal delivery	Ex vivo date confirmed NPs were able to penetrate the mucosal layer, be absorbed by goat nasal epithelium, and reach the submucosal layers. This innovative system shows promise as a vehicle for nasal drug delivery aimed at targeting the brain. The concentration of carmustine was significantly lower in blood plasma compared to brain plasma for the intranasally administered formulation. It demonstrated a slower release of the drug from the formulation and permeation of the nanoparticles and drug across the nasal mucosal membrane at various time intervals, which contributes to improved uptake in the brain.	in vitro U87 glioma cells; pharmacokinetic study in Wistar rats	42
magnetic graphene oxide and chitosan-coated NPs loaded with DOX	126−174 nm	spherical particles	mGO, −7.4 mV; mGOC, +37.9 mV; mGOCG, +24.1 mV	•chitosan-functionalized •magnetic guided targeting •PEGylation	Intravenous infusion of these nanoparticles resulted in significant tumor accumulation, inhibited tumor growth, and improved survival in a U87MG orthotopic cancer mouse model. Moreover, applying a magnetic field during treatment further enhanced these results by facilitating targeted delivery of DOX to the brain.	mice orthotopic U87MG model	43
polystyrene NPs	20−50 nm	spherical particles	neutral and positively charged	surface charge	enhanced NP permeability across BBB through electrostatic interaction	in vitro BBB model (bEnd3 cells)	44
dendrigraft poly(L-lysine)-based siRNA and D peptide nanoparticles	110 nm	spherical particles	slightly positive charge	T7 peptide for BBB targeting; Tet1 peptide for neuron targeting	significant reduction in amyloid-β plaques; improved cognition in AD mice	AD animal model (APP/PS1 transgenic mice)	45
methoxypoly(ethylene glycol)-*b*-poly(caprolactone) and chitosan-alginate nanocomplexes	400−500 nm	spherical particles	RH/PCL−PEG/CS, +34 mV; RH/CS-ALG, +40 mV	mucoadhesive coating with chitosan and alginate	elevated brain targeting via intranasal delivery; higher RH bioavailability	Parkinson's disease animal model (swiss albino mice)	46
quercetin-modified sulfur nanoparticles (Qc@SNPs-MB) with microbubbles	50 nm to 2.1 μm	spherical particles	−38.4 mV	FUS for BBB penetration; ultrasound pressure of 1000 kPa; treatment duration of 5 min	improved memory and learning abilities in AD mice	AD animal model (20 AD mice)	47
diselenide bond-containing ROS-responsive ruthenium nanoplatform	70 nm	spherical particles	N/A	NIR-triggered photothermal and ROS-responsive release	promotion of neurite outgrowth and reduction in amyloid-β	AD model with neuron regeneration focus	48
rhynchophylline-loaded mPEG−PLGA nano-	120 nm	spherical particles	slightly negative and	mPEG−PLGA coating for enhanced BBB crossing	efficient brain targeting and neuroprotective effects for AD treatment	AD in vitro model (Neuro2a cells)	49

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Table 1. continued

nanosystem	size	shape	ζ potential	strategies	important findings	disease model	refs
particles coated with Tween-80			neutral charge				
magnetic nanoparticles with external electro-magnetic field	500 nm	spherical particles	N/A	external magnetic field steering for targeting deep brain regions; magnetic gradient determined by actuator currents ranging from 0.5 to 3 A	controlled MNP aggregation in deep brain areas	AD deep brain model (Streptozotocin-induced AD rat model)	50
rapamycin and BACE1 siRNA-loaded dendrigraft poly(L-lysine) nanoparticles	129.6 nm	spherical particles	+7.68 mV	intranasal administration; AAL and KLVFF peptide targeting for brain delivery	reduced amyloid-β deposition and improved cognition in AD mice	AD animal model	52
CS/GQD nanoparticles	4−20 nm	spherical particles	−96.3 mV	microfluidic synthesis for size control; intranasal delivery	enhanced brain targeting and memory improvement in AD rat model	AD rat model	53
DOX-loaded PLGA NPs	110 nm	spherical particles	slight negatively charged	PLGA NPs	penetration of both the intracranial tumor and normal brain tissue after i.v. infusion	orthotopic GBM rat model	54
ferritin-based nanovectors	12 nm	spherical particles	N/A	•transferrin receptor targeting •intranasal	NPs can cross the BB, reduce tumor growth, and improve survival in mice	orthotopic GBM mice model	55

substances from passing through. This structure is essential for maintaining the brain's homeostasis but also limits the entry of therapeutic agents.

Additionally, the BBB exhibits selective permeability, allowing only certain small molecules (<400 Da) and lipophilic (fat-soluble) substances to cross. As a result, many potential drugs—especially larger molecules, hydrophilic (water-soluble) compounds, and biologics like proteins—struggle to penetrate the barrier.[29] The BBB also employs active transport mechanisms designed to remove toxins and unwanted substances. Unfortunately, these systems can also expel therapeutic drugs, reducing their effectiveness and concentration in the brain. While there are some transporters, such as those for glucose and amino acids, that facilitate the movement of specific nutrients, these pathways are often unsuitable for delivering larger therapeutic molecules.[30]

Another challenge is the potential for neurotoxicity. Even if a drug successfully crosses the BBB, it may have unintended effects on brain tissue, raising concerns about safety during drug delivery.[31] Moreover, the integrity and function of the BBB can vary among individuals and under different disease conditions.[32] Factors such as inflammation or neurodegeneration can alter BBB permeability, complicating drug delivery strategies. Finally, once a drug crosses the BBB, it must reach its target cells and achieve therapeutic concentrations without causing side effects. This necessitates precise formulations and effective delivery methods.[33]

The BBB poses significant challenges for drug delivery to the brain. While the BBB is crucial for protecting the brain from potentially harmful substances, it also limits the entry of therapeutic drugs.[34] To deliver drugs to the brain safely and effectively, several noninvasive strategies have been developed to overcome the BBB.[35] Therefore, overcoming this challenge by designing suitable nanocarriers to transport therapeutics through BBB has become an urgent necessity. Employing nanocarriers for drug transportation is an effective approach, as they can deliver a variety of payloads, including anticancer agents, proteins, nucleic acids, etc., to multiple targeted sites and simultaneously protect them from premature degradation or release.[36,37] Figure 1 illustrates strategies based on polymeric nanoparticles to cross the BBB.

3. STRATEGIES

3.1. Major Polymers in NP-Based Brain Cancer and Neurodegenerative Studies. The main guiding principles for the development of polymeric NPs are that they are safe and effective by being biodegradable, biocompatible, nontoxic, and nonimmunogenic. Cost considerations play a role, too. Both synthetic and natural polymers are used for brain delivery. Within the group of synthetic polymers are included: poly(alkylcyanoacrylate) (PACA), poly(lactide-*co*-glycolide) (PLGA), poly(ethylene glycol) (PEG), poly(ε-caprolactone) (PCL), and poly(lactic acid) (PLA), which were approved by the U.S. Federal Drug Administration for pharmaceutical purposes. Among these, PLGA is the most frequently used synthetic polymer for both cancer and neurodegenerative applications.

3.1.1. Poly(lactide-co-glycolide) (PLGA). PLGA is commonly employed in microsphere and microparticle drug delivery systems and serves as a versatile platform for nanoparticle-based therapies. This is due to its advantageous properties, such as simple biodegradability, ease of synthesis, tunability, commercial availability, sustained drug release, and biocompatibility.

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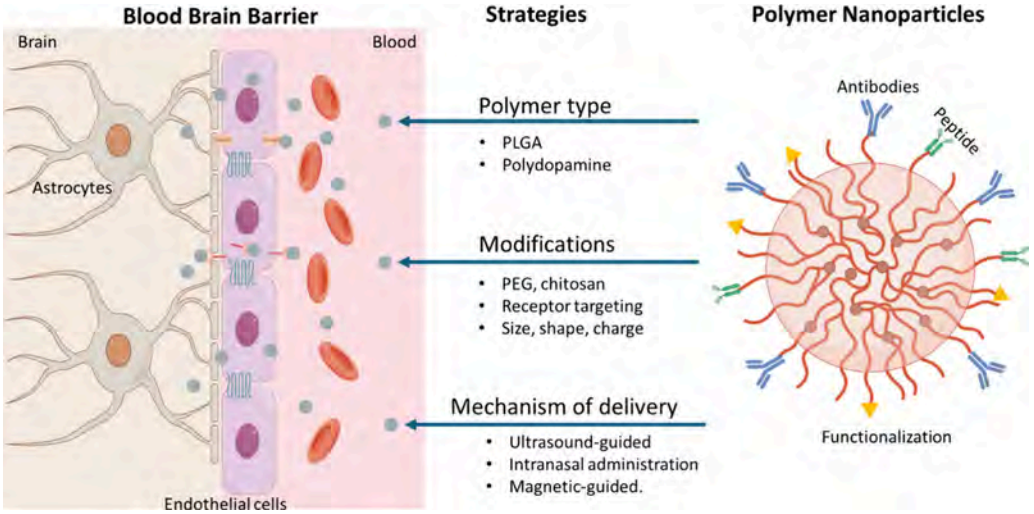

Figure 1. Strategies of polymer nanoparticles for navigating the BBB.

Table 2. Comparative Evaluation of Polymeric Nanoparticles for Brain Drug Delivery: Biodegradability, Toxicity, and BBB Penetration Efficiency

polymeric nanoparticle	biodegradability (half-life, days)	toxicity (cytotoxicity IC50, μg/mL)	BBB penetration efficiency (%)	advantages	limitations	ref
PLGA	10−50	>100	∼20−30	biocompatible, widely used, controlled drug release	requires surface modifications for BBB targeting	13
dopamine-based	varies (depending on the polymer structure)	50−100	∼40−50	mimics endogenous dopamine, high affinity for dopamine transporters	potential oxidation, requires stabilization	95
chitosan	1−5	>100	∼25−35	mucoadhesive properties, enhances nasal drug delivery	limited intrinsic BBB penetration, needs functionalization	96

Recent research has highlighted the effectiveness of PLGA NPs in crossing the BBB for neurodegenerative disease and brain cancer treatment. PLGA NPs have shown success in delivering neuroprotective and chemotherapeutic agents to brain tissues, enhancing therapeutic outcomes in animal models of Alzheimer's, Parkinson's, and brain cancer diseases.[56]

In AD treatment, Tripathi and co-workers synthesized donepezil-loaded PLGA nanoparticles using a modified nanoprecipitation method to enhance drug transport across the BBB. Their results demonstrated that loading donepezil onto PLGA significantly improved its uptake by brain endothelial cells compared to the free drug, indicating its enhanced therapeutic potential in Alzheimer's treatment due to their favorable size and sustained release properties.[57] Another study developed mPEG−PLGA nanoparticles loaded with Rhynchophylline for the potential treatment of AD. Experimental data revealed that the NPs had a brain uptake rate of approximately 12% in animal models, significantly higher than Rhynchophylline alone, which showed minimal BBB penetration. Additionally, fluorescence tracking in vivo confirmed that the NPs were able to accumulate in brain tissues, particularly in regions associated with neurodegeneration in AD. The study confirmed that these nanoparticles could effectively cross the BBB, exhibit neuroprotective effects, regulate neuron activity in vitro and exhibited a potential to be an alternative drug for the treatment of AD.[49]

In brain cancer application, recent research by Maksimenko et al. demonstrated that doxorubicin (DOX)-loaded PLGA nanoparticles, coated with poloxamer 188 (a copolymer surfactant known for its cell-repairing capabilities), effectively penetrated the BBB and intracranial tumors, resulting in significant antitumor effects in vivo.[54] Another study showed that PLGA nanoparticles loaded with the chemotherapeutic drug morusin and conjugated to chlorotoxin (a peptide targeting specific chloride channels in glioma cells) exhibited notable antitumor activity against two human GBM cell lines in vitro. Similar in vitro results with various modified PLGA nanoparticles have been reported recently, and their application in brain tumor-bearing rodent models has also been promising.[41] The extensive literature highlights the potential of PLGA-based nanocarrier systems for treating CNS tumors through specific surface modifications and loading contents.

3.1.2. Dopamine Polymers. Dopamine is a critical neurotransmitter affected in diseases like Parkinson's, where dopaminergic neurons are progressively lost.[58] Dopamine-based polymers, such as those described by Trapani et al.,[59] can be designed for intranasal delivery, which is a noninvasive route that bypasses the BBB entirely. Intranasal administration leverages the olfactory and trigeminal nerve pathways to transport drugs directly to the brain. Dopamine polymers, conjugated with carriers like *N,O*-carboxymethylchitosan, demonstrated stability and efficacy in nose-to-brain delivery, providing high dopamine loading and effective uptake by olfactory ensheathing cells. This mechanism avoids systemic circulation and potential degradation, making it a promising option for delivering therapeutic dopamine directly to the brain for neurodegenerative conditions.[59]

Dopamine polymers can be designed to respond to specific environmental triggers within the brain, such as pH or ROS levels. For instance, polydopamine-based nanoparticles[60,61] are inherently bioactive materials with strong metal-ion chelating and ROS scavenging properties. These properties allow them to reduce ROS levels and protect cells from oxidative stress, which

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is often elevated in neurodegenerative diseases. This responsiveness allows for controlled, localized release of the therapeutic cargo precisely where it is needed, reducing systemic toxicity and improving therapeutic efficacy.[62,63]

While polymeric nanoparticles such as PLGA, dopamine-based, and chitosan nanoparticles offer promising strategies for drug delivery across the BBB; their safety and long-term effects remain critical concerns (Table 2). PLGA nanoparticles are generally considered biocompatible and biodegradable, but the byproducts of their degradation (lactic and glycolic acid) may cause local pH changes, potentially leading to cytotoxicity with prolonged use.[64] Dopamine-based nanoparticles, while effective in mimicking endogenous neurotransmitter functions, face challenges related to oxidative stress and neurotoxicity, as free dopamine and its metabolites can contribute to ROS formation, leading to neuronal damage if not properly stabilized.[61] Chitosan nanoparticles, known for their mucoadhesive and biocompatible properties, can enhance drug absorption but may trigger immune responses due to their cationic nature, potentially leading to inflammation or unwanted immune activation.[65] Additionally, concerns about long-term accumulation of nanoparticles in the brain remain unresolved, as inefficient clearance mechanisms could lead to nanoparticle buildup, affecting normal neuronal function.[66] Future studies must focus on biodegradability optimization, immune system interactions, and nanoparticle clearance pathways to ensure that these delivery systems remain both effective and safe for prolonged clinical use.[61]

3.2. General Modifications. *3.2.1. Poly(ethylene glycol) (PEG).* PEG is a hydrophilic polymer that can be covalently linked to NPs and other therapeutics to enhance their circulation time in the body. The FDA classifies PEG as Generally Regarded as Safe, and since 1990, several PEGylated protein therapeutics have received FDA approval. By conjugating PEG to the surfaces of NPs, their recognition by immune cells is reduced due to decreased protein adsorption, which is achieved through steric hindrance, ultimately increasing their bioavailability.[67] Specifically, PEGylated NPs demonstrate fewer interactions with plasma proteins and cell membranes compared to non-PEGylated counterparts, making them more resistant to aggregation, opsonization, and phagocytosis.[68] Supporting its safety profile, PEGylation of NPs has not been linked to increased toxicity and remains one of the most widely used modifications for improving the efficacy of nanotherapeutics.[68,69]

While PEGylation reduces immune recognition, it does not necessarily improve targeting specificity.[70] The presence of PEG can hinder receptor-mediated targeting, which may limit its effectiveness for some specific therapies. Although PEG is generally considered safe, repeated use of PEGylated nanoparticles may induce immune responses in some individuals, especially after multiple doses. PEGylation is highly effective for drugs that require prolonged circulation in the bloodstream, such as certain chemotherapeutic agents or biologics (e.g., monoclonal antibodies). However, for drugs that need highly specific tissue targeting, other surface modifications might be more suitable.

3.2.2. Polydopamine. Dopamine polymers can be engineered with surface modifications to enhance their ability to cross the BBB. Surface functionalization with polydopamine, as shown in the Gao et al. study, provides a robust platform for additional targeting ligands or responsive coatings. Polydopamine modification enhances nanoparticle penetration across the BBB, which is particularly important for treating neurodegenerative diseases. Polydopamine can be used for both its adhesive properties and its ability to respond to external stimuli, such as near-infrared (NIR) light. In this study, the nanoparticles coated with polydopamine and activated by NIR radiation showed improved BBB penetration and uptake by dopaminergic neurons, delivering therapeutic agents to treat Parkinson's disease more effectively. The ability to respond to NIR light also allows for localized targeting within the brain, reducing off-target effects and enhancing treatment specificity.[60] While NIR activation is a promising technique, prolonged exposure to NIR light may pose safety concerns for the surrounding healthy tissues, especially with extended treatment protocols. Despite promising preclinical results, there is limited clinical translation of Polydopamine-coated nanoparticles, and further studies are needed to fully assess their safety and efficacy. Polydopamine modification is highly suitable for neurotherapeutic drugs, especially those that need to be delivered to specific brain regions. Drugs like dopamine agonists, antiamyloid agents, and neuroprotective compounds benefit from PDA's BBB penetration and NIR-responsive characteristics.

3.2.3. Chitosan. Chitosan-coated nanoparticles have shown significant promise for delivering drugs to the brain. As a natural polymer widely used and approved for human applications, chitosan is biodegradable, biocompatible, nontoxic, nonallergenic, and cost-effective, making it an ideal material for medical use.[71−77] Many studies have explored chitosan-coated nanosystems for delivering therapeutic compounds aimed at treating conditions such as AD, Parkinson's disease, gliomas, cerebral ischemia, and schizophrenia.[38,40,43,61,78] The positive charges of chitosan and its ability to act as a cationic polyelectrolyte offer three advantages to brain drug delivery. First, the mucoadhesive property that creates an interface of electrostatic interaction with the negative charges of the glycocalyx and the phospholipids of the epithelial membrane in the BBB.[79] Second, it promotes enhanced permeation by facilitating the opening of tight junctions.[80,81] Third, its ability to coat surfaces and enhance the properties of other materials, such as producing positive ζ potential that improves the stability of nanosystems in physiological conditions.[38]

Research has shown that chitosan-modified PLGA nanoparticles, loaded with chemotherapeutic drugs, effectively target GBMs and brain cancer in both in vitro and in vivo models.[38,82,83] These recent studies revealed that chitosan-coated nanoparticles exhibit increased cytotoxicity against malignant cells, improved selectivity, enhanced absorption by cancer cells, and better penetration into brain tissue. The benefits of chitosan are attributed to its ability to promote mucoadhesion, which extends the system's residence time in the olfactory mucosa, facilitate electrostatic interactions with BBB cells, open tight junctions, and regulate the drug release rate. Additionally, some nanoparticles have been functionalized with sialic acid to aid BBB permeability, or with antialdehyde dehydrogenase or folic acid to specifically target brain cancer stem cells.[84]

Chitosan nanoparticles have also been proposed to exhibit antitumor properties against glioma cells, as indicated by their impact on various signaling pathways and molecules. Chemotherapeutic drugs targeting gliomas have been loaded into these nanoparticles, which are reported to outperform pure therapeutic agents. This enhanced effectiveness is attributed to several factors, including sustained drug release, improved drug internalization, and increased cytotoxicity toward cancer cells.

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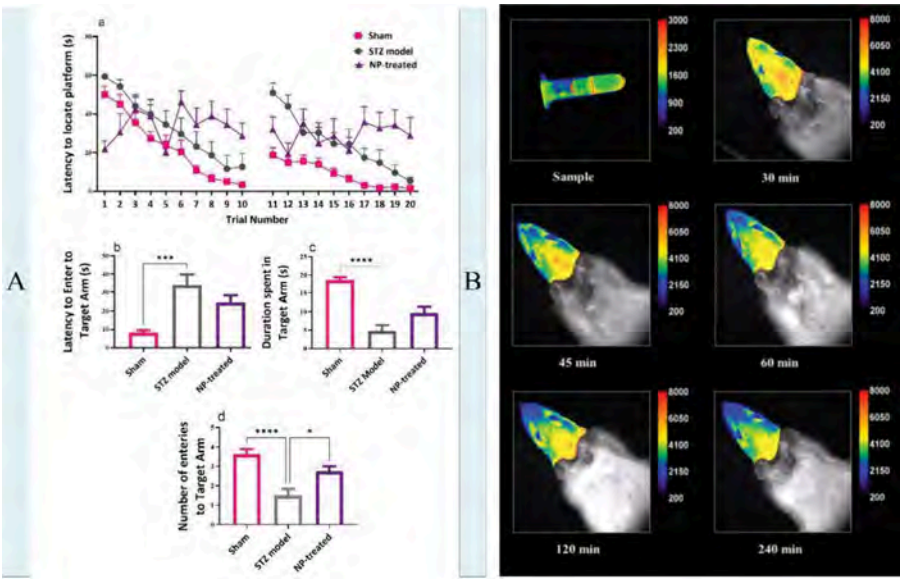

Figure 2. (A) Effect of IN delivery of CS/GQD NPs on the memory of STZ-induced Alzheimer's-like model rats in a RAWM test: (a) effect of the NPs on latency to locate the platform on training days; (b) effect of the NPs on latency to enter the target arm in probe day; (c) effect of the NPs on the duration of the presence in the target arm in probe day; (d) effect of the NPs on the number of entrances into the target arm in probe day. To define whether the data were normal, the D'Agostino and Pearson normality test was used. Experimental results were provided as mean ± standard error of the mean. One-way and two-way analyses of variance followed by Tukey's and Bonferroni's post hoc multiple comparison tests were used, respectively. The differences with $p < 0.05$ were regarded as significant. To examine the differences between groups, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$ were compared to the control group ($n = 8$ in all groups). (B) In vivo fluorescence images of CS/GQD NPs distribution in the brain at different time points after IN delivery. The excitation and emission filters were set to 470 and 535 nm, respectively. Reproduced with permission from ref 53. Copyright 2023 John Wiley and Sons.

Recent studies have demonstrated the effectiveness of chitosan-coated nanoparticles in crossing the BBB and delivering therapeutic agents for neurodegenerative diseases. In the ropinirole hydrochloride-loaded chitosan nanoparticle study for Parkinson's disease,[46] the nanoparticles exhibited a particle size of 240 nm, and a positive ζ potential of 36.8 mV, which improved their adhesion to the nasal mucosa and facilitated enhanced permeability through the nasal route, bypassing the BBB. After intranasal administration, the brain-to-blood concentration ratio was significantly higher for the chitosan-coated nanoparticles compared to uncoated formulations. Specifically, at 1-h postadministration, the Cmax (maximum concentration) of ropinirole in the brain was 2.8 ± 0.3% of radioactivity/g for the chitosan nanoparticles, compared to 0.93 ± 0.03% for noncoated versions. This data demonstrates that the chitosan coating not only helped in crossing the BBB but also significantly increased drug accumulation in the brain.

Another study on chitosan/graphene quantum dots (CS/GQD) nanoparticles for AD treatment demonstrated that these nanoparticles can effectively cross the BBB and accumulate in the brain.[53] In vivo bioimaging confirmed the distribution of the CS/GQD nanoparticles in the brain after intranasal administration, with fluorescence signals observed as early as 30 min postadministration (Figure 2). The nanoparticles were widely distributed across the brain within 2 h. Additionally, transmission electron microscopy (TEM) images showed that the nanoparticles were internalized in myelinated axons of hippocampal neurons, further confirming their BBB penetration. These nanoparticles also demonstrated a significant improvement in memory recovery in Alzheimer's-like rats, as evidenced by the radial arm water maze (RAWM) test, with treated rats making more successful entries into the target arm compared to controls.

Overall, chitosan is particularly effective for drugs targeting gliomas, Alzheimer's, and Parkinson's disease due to its ability to cross the BBB and its versatile drug delivery properties. Its use with chemotherapeutics, like in glioma treatments, has shown promising results. For neurodegenerative diseases, its biocompatibility makes it an ideal choice for chronic treatment regimens.

3.2.4. Receptor Targeting. NPs can be engineered to exploit various transport mechanisms, including adsorptive-mediated transcytosis (AMT), receptor-mediated transcytosis (RMT), and cell-based delivery. AMT relies on electrostatic interactions between positively charged ligands and the negatively charged membranes of brain capillary endothelial cells. While NPs can potentially leverage this process, its role in the delivery of endogenous compounds through the BBB remains uncertain. In contrast, RMT is one of the most established strategies for enhancing drug delivery to brain tissue. This process involves receptor-mediated endocytosis on the luminal side of the BBB, followed by the trafficking of NPs through endothelial cells and their eventual release into the brain parenchyma. Key targets for RMT include the transferrin receptor (TfR) which is highly expressed in GBM cells, making them promising targets for improving NP delivery through both the BBB and directly to brain tumors. TfR is particularly favored for targeting therapeutics via RMT because it is expressed on brain capillary endothelial cells but not on endothelial cells elsewhere in the body. Various ligands can be conjugated to NPs for targeting TfR, including transferrin, antibodies, and specific peptides. Cai et al. designed a nanoparticle based on dendrigraft poly(L-lysine) (DGL) that carries siRNA and D peptides which target and penetrate the BBB, enter the brain and accumulate in AD lesions. The T7 peptide, which specifically targets TfR on the BBB, is attached to DGL using an acid-cleavable long-chain PEG

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(MW 6000) which enhances internalization, allows for quick escape from endo/lysosomes, and promotes effective transcytosis. As a result, the production of β-amyloid plaques (Aβ) is inhibited, neurotoxicity caused by Aβ plaques and phosphorylated tau (p-tau) tangles is reduced, and cognitive function in AD mice is significantly improved. Overall, this system effectively targets the BBB and neurons, enhancing drug accumulation in the brain and improving treatment outcomes for AD.[45]

In brain cancer application, Ramalho et al. demonstrated enhanced internalization of TMZ-loaded PLGA NPs coated with monoclonal antibodies against TfR (specifically OX26) in GBM cells via receptor-mediated endocytosis.[85] Their findings showed high tumor targeting efficiency in vitro, along with increased cellular uptake, slower tumor growth, improved median survival, and enhanced antitumor effects in vivo.

Glycoproteins such as rabies virus glycoprotein (RVG) and penetratin (Pen) peptides have also proven useful in delivering drugs specifically to areas affected by AD. Another example is the functionalization of nanoparticles with amyloid-β targeting peptides (FPLIAIMA), which has shown success in Alzheimer's mouse models.[86] Mitochondria-targeted nanoparticles are gaining attention for their potential to address mitochondrial dysfunction, a key factor in neurodegenerative diseases like Parkinson's and Alzheimer's. These nanoparticles can be functionalized with C3 or RVG29 peptides or ligands, such as triphenylphosphonium, which directs them to the mitochondria to counteract oxidative stress and promote neuronal survival.[87]

A key challenge, however, is the saturation of receptor-mediated pathways, which can reduce nanoparticle uptake after repeated doses. Additionally, rapid clearance by the mononuclear phagocyte system (MPS) limits the circulation time of these functionalized nanoparticles, reducing overall bioavailability[88,89] To address these issues, future approaches should optimize ligand density and employ surface modifications like PEGylation to prolong circulation time while minimizing MPS recognition.

3.2.5. Size, Shape, and Charge. Nanoparticle size, shape and charge play pivotal roles in their ability to traverse the BBB and effectively deliver therapeutic agents to brain tissues. The BBB is highly selective and restricts the passage of most substances, especially large and charged molecules. Optimizing nanoparticle properties, specifically size, shape and charge, can significantly enhance their permeability across this barrier. Generally, nanoparticles smaller than 200 nm are considered optimal for BBB penetration as they are efficiently transported through endocytosis.[16,44,56]

Moreover, nanoparticle charge is equally important. Positively charged nanoparticles have been shown to interact more favorably with the negatively charged endothelial cells lining the BBB. This interaction enhances cellular uptake through AMT, a process where electrostatic attraction between positively charged nanoparticles and the cell membrane facilitates the crossing of the BBB. However, a high positive charge can increase cytotoxicity and promote rapid clearance by immune cells. The specific charge threshold that would lead to increased toxicity or rapid immune clearance is not universally fixed and can depend on factors like the type of nanoparticles, the target cells, and the experimental conditions. However, in general, a high positive charge (e.g., + 30 mV or higher) tends to increase the likelihood of toxicity, as the particles are more likely to interact with negatively charged cell membranes, leading to cell membrane disruption and higher cellular uptake, which can result in cytotoxicity.[90,91] Balancing the charge is therefore crucial for maximizing brain uptake while minimizing adverse effects.[92]

The shape of nanoparticles also plays a significant role in their ability to cross the BBB. Spherical nanoparticles typically offer good stability and can cross the BBB through receptor-mediated endocytosis or RMT. However, their ability to penetrate the BBB may be less efficient than other shapes, depending on the targeting and delivery mechanisms employed. Rod-shaped nanoparticles, on the other hand, may demonstrate improved BBB penetration compared to spherical ones. Their elongated shape allows for greater interaction with cell membranes, potentially enhancing their ability to cross the BBB via endocytosis. Additionally, rod-shaped nanoparticles offer a larger surface area, which may increase cellular uptake. In agreement to this, studies involving polystyrene nanorods decorated with targeting moieties have shown that rod-shaped particles exhibit stronger adhesion and enhanced internalization in comparison to its spherical counterparts by brain endothelial cells, both under static and flow conditions in microfluidic device.[93,94] In the treatment of neurodegenerative diseases, nanoparticles within the optimal size range have demonstrated promising results. Zhang et al. explored different nanoparticle sizes and found that particles around 50 nm achieved high BBB permeability. They discovered that positive surface charge significantly enhanced the permeability and uptake of nanoparticles in brain endothelial cells in vitro, resulting in higher concentrations within target regions. This size and charge optimization approach is particularly valuable for delivering small interfering RNA (siRNA) and other neuroprotective agents for AD, as evidenced by increased target engagement and cognitive improvements in animal models.[44]

For brain cancer applications, studies have demonstrated that polymeric nanoparticles customized for size and charge can improve drug penetration and retention within tumors. In a mouse model of traumatic brain injury, Rabanel et al.[56] examined PEG-coated PLGA nanoparticles of varying sizes and found that 100 nm particles exhibited prolonged circulation times and superior brain penetration compared to larger particles of 200 and 800 nm. This suggests that a 100 nm size range may facilitate prolonged interaction with the brain endothelium, promoting deeper parenchymal distribution. Similarly, Nowak et al.[93] tested spherical polystyrene nanoparticles and found that 200 nm particles were more effective in BBB penetration compared to 100 and 500 nm particles in a microfluidic model, highlighting the size-dependent nature of nanoparticle transport mechanisms across the BBB.

Overall, nanoparticle size, shape and charge are critical for crossing the BBB and delivering therapies to the brain. Nanoparticles within the 100−200 nm size range are considered optimal, as they are small enough to cross the BBB through endocytosis but large enough to avoid rapid renal clearance. Positively charged nanoparticles enhance transport by interacting with the negatively charged endothelial cells lining the BBB, although excessive positive charge may increase cytotoxicity and immune clearance. In neurodegenerative diseases, these size and charge-optimized nanoparticles have shown promise in delivering agents like siRNA, improving brain targeting and therapeutic outcomes. For brain cancer, studies demonstrate that nanoparticles around 100−200 nm improve drug delivery within tumors, achieving greater penetration and retention. This size and charge specificity supports the development of more effective and targeted brain therapies for both neurodegener-

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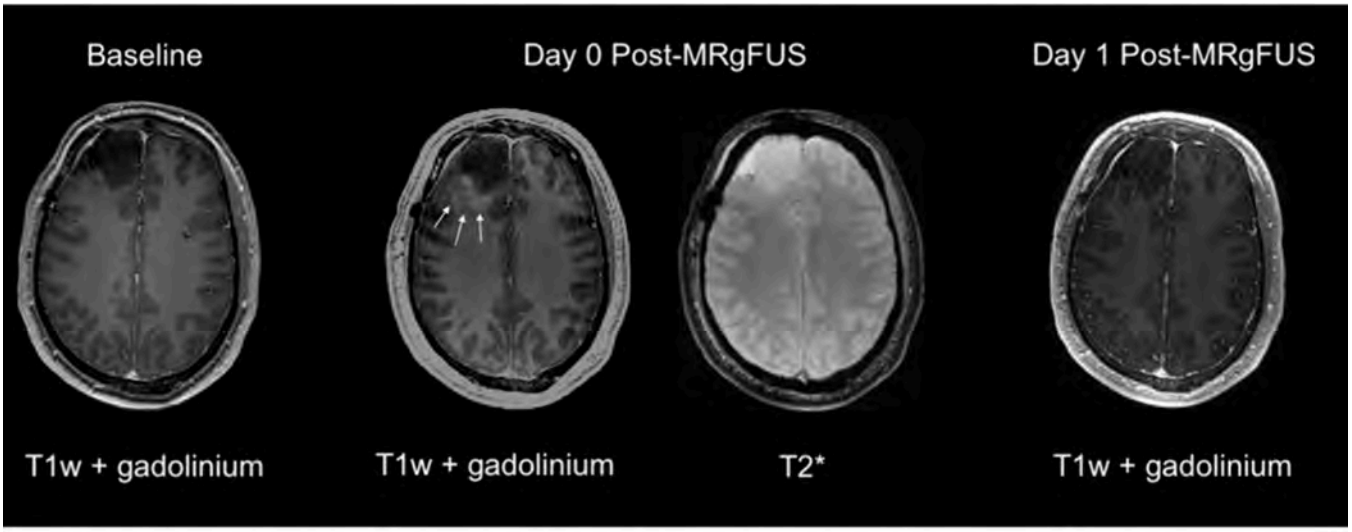

Patient	Sonicated volume (mm^3)	Sonication power (W)	% Enhancement	Chemotherapy concentration in peritumor tissue	
				sonicated (ng/mg)	unsonicated (ng/mg)
1	486 × 2	5–9	40 ± 11	0.22	0.15
2	486 × 4	6–7.5	—	—	—
3	486 × 5	8–10	50 ± 22	—	—
4	486 × 2	6–7.5	15 ± 5	3.47×10^{-4}	0.45×10^{-4}
5	486 × 5	4–15	35 ± 15	—	—

Figure 3. MRI of BBB disruption. The BBB was safely and successfully opened in the five patients enrolled, as shown by postsonication gadolinium enhancement in the target region and resolution 24 s. Sample T1-weighted postgadolinium MRI from patient five obtained 30 days prior to BBB opening procedure (left), immediately following BBB disruption (middle), and 20 h after BBB disruption (right). Ill-defined contrast enhancement is seen in the peritumoral region on images acquired immediately after MRgFUS (white arrows). This contrast enhancement has resolved in the peritumor region on the day 1 follow-up image indicating closure of the BBB. T2* sequence acquired immediately following BBB disruption for this patient show no evidence of microhemorrhages. The table indicates the percent change in signal intensity in the region of interest (sonicated) relative to adjacent nonenhancing tumor margin tissue in the ipsilateral hemisphere. Reproduced from ref 25. Available under a CC-BY license.

ative and cancerous conditions. Moreover, PLGA nanoparticles exhibit high biodegradability (10−50 days) and low cytotoxicity (IC_{50} > 100 μg/mL), but typically show moderate BBB penetration (∼20−30%) unless surface-modified.[13] Dopamine-based nanoparticles, inspired by neuromelanin structures, demonstrate improved BBB penetration efficiency (∼40−50%) due to their affinity for dopamine receptors and transporters, although their stability and oxidative sensitivity can pose challenges.[95] Chitosan nanoparticles, with a biodegradability half-life of ∼1−5 days and cytotoxicity >100 μg/mL, are notable for their mucoadhesive properties and suitability for intranasal administration, though their intrinsic BBB penetration is moderate (∼25−35%) without functionalization.[96]

3.3. Mechanism of Delivery. Many strategies have been developed to enhance drug delivery across the BBB, each with unique advantages and challenges. Ultrasound-mediated delivery, intranasal administration, and magnetic nanoparticle systems offer innovative approaches, differing in their targeting precision, invasiveness, and scalability.

3.3.1. Ultrasound-Guided Nanoparticle Delivery for BBB Disruption. Ultrasound-guided nanoparticle delivery has emerged as a promising noninvasive approach for crossing the BBB. This method typically utilizes FUS in combination with microbubbles to temporarily disrupt the BBB, enabling nanoparticle-based drugs to reach targeted brain regions. The mechanism involves acoustic cavitation, where microbubbles oscillate and collapse in response to ultrasound waves. This activity transiently widens the tight junctions between endothelial cells, creating localized openings in the BBB that allow therapeutic agents to penetrate the brain tissue. The process is highly controlled, with the BBB generally closing within a few hours post-treatment, thus maintaining the barrier's protective function elsewhere.[97]

In the realm of neurodegenerative diseases, such as Alzheimer's, FUS has been evaluated in clinical settings to facilitate drug delivery to affected brain regions. A study by Liu et al. used low-intensity FUS to disrupt the BBB in conjunction with quercetin-modified sulfur nanoparticles, aimed at relieving

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endoplasmic reticulum stress—a key factor in Alzheimer's pathology. The results showed improved delivery and accumulation of nanoparticles in brain tissues, specifically in the hippocampus and cortex, which are critical areas for Alzheimer's treatment.[47] While promising, challenges remain in refining ultrasound parameters to avoid off-target effects and ensure consistent BBB disruption.

Clinical trials are assessing the use of ultrasound-guided BBB disruption to improve drug delivery in AD patients. A recent study by Rezai et al. involved an open-label trial where ten participants with mild Alzheimer's underwent MRI-guided FUS (MRgFUS) treatments targeting the hippocampus, entorhinal cortex, frontal, and parietal lobes. Each patient received three treatment sessions spaced 2 weeks apart, focusing on β-amyloid-positive regions. Results showed that all participants experienced temporary BBB opening with subsequent closure within 24−48 h after each session. At 6−12 months post-treatment, no significant adverse effects were observed, and PET imaging demonstrated a 14% reduction in β-amyloid plaque load in the treated regions. Cognitive assessment scores remained stable, with no observable cognitive decline beyond the typical progression of Alzheimer's, indicating a potential disease-modifying effect.[98]

For brain cancer treatment, particularly in cases of GBM, ultrasound-guided BBB disruption has shown potential to enhance chemotherapy delivery. A notable example is a phase I clinical trial that assessed MR-guided FUS in conjunction with microbubbles to disrupt the BBB in glioma patients (Figure 3). In this trial, Mainprize et al. used the ExAblate Neuro system; an integrated FUS device that uses MRI to guide ultrasound waves to a targeted location in the brain, which allowed precise BBB disruption, followed by administration of chemotherapeutic agents like liposomal DOX and TMZ. Ongoing clinical trials are exploring various FUS systems for BBB disruption in glioma patients. The ExAblate Neuro system, recently approved by the FDA for thalamotomy, allows for targeted BBB disruption in small areas of the brain using FUS in conjunction with standard MRI scanners. Two phase I trials are currently recruiting participants.

Post-treatment analysis confirmed higher concentrations of these agents in the brain regions where the BBB had been disrupted, as observed through increased gadolinium enhancement on MRI. Patients tolerated the procedure well, and tumor resection surgery performed the following day confirmed the localized distribution of chemotherapy drugs.[25]

A recent trial (NCT02253212[99]) examined the safety and efficacy of the SonoCloud-1 device, also using low-intensity pulsed ultrasound with microbubbles, in 21 patients with recurrent GBM. Nineteen patients received at least one ultrasound treatment. BBB disruption was confirmed via MRI after 52 out of 65 ultrasound sessions, and the treatment was deemed safe, with no serious adverse events. Patients who experienced successful BBB disruption had longer progression-free survival (4.11 months) and overall survival (12.94 months) compared to those with poor or no disruption. Overall, SonoCloud-1 treatments were well tolerated and may increase the effectiveness of systemic drug therapies, such as carboplatin, in the brain without inducing neurotoxicity. Additionally, recent trials in Alzheimer's and Parkinson's disease patients have shown promising results, supporting MRgFUS as a safe method for enhancing drug permeability across the BBB.[100] These findings indicate that ultrasound-mediated BBB disruption holds great potential for improving targeted drug delivery in neurodegenerative diseases while minimizing systemic side effects.

In summary, ultrasound-guided nanoparticle delivery is a noninvasive approach to temporarily disrupt the BBB for targeted drug delivery. Using FUS with microbubbles, this technique opens the BBB through acoustic cavitation, allowing nanoparticles to enter the brain and deliver therapeutic agents to specific areas. In neurodegenerative diseases like Alzheimer's, FUS has shown promise in increasing the brain delivery of nanoparticles that reduce amyloid-β accumulation, potentially modifying disease progression. For brain cancer, such as GBM, FUS facilitates chemotherapy delivery, enhancing drug concentration in tumors and extending survival. Although ultrasound-guided delivery demonstrates strong potential, it requires precise control of ultrasound parameters and further research to ensure safety and consistent BBB disruption. Although FUS allows targeted drug delivery, its penetration depth is often limited, which can be a problem for brain regions deep within the skull. Additionally, it requires specialized equipment (MRI, ultrasound systems), which may limit accessibility and increase costs. Although the temporary BBB opening is beneficial in some cases, it might be inadequate for chronic treatments. FUS is particularly useful for large molecules or nanoparticles that would otherwise struggle to cross the BBB. It is most effective for drugs that need targeted, localized delivery (e.g., chemotherapy for GBM, amyloid-β-targeting antibodies for Alzheimer's). Drug modifications to ensure stability and controlled release (e.g., liposomal formulations) are beneficial when using this technique.

3.3.2. Intranasal Administration. While ultrasound-guided drug delivery provides a noninvasive and transient method to open the BBB, its reliance on microbubbles and precise sonication parameters makes it more suitable for targeted drug release rather than continuous or systemic drug administration. However, for a less invasive and more patient-friendly alternative, intranasal drug delivery offers a promising route by bypassing the BBB naturally via neural pathways, allowing for direct brain access without external energy application. Although it lacks the precise spatial targeting of ultrasound methods, intranasal delivery is advantageous for frequent dosing and biologics such as peptides and proteins that might be degraded in systemic circulation.

Intranasal administration is a noninvasive delivery method that leverages the olfactory and trigeminal nerve pathways to deliver drugs directly to the brain, effectively bypassing the BBB. This delivery route is particularly advantageous for targeting CNS diseases, as it reduces systemic circulation exposure, minimizes off-target effects, and enhances drug concentrations in brain tissues. However, intranasal delivery faces challenges such as enzymatic degradation in the nasal passages and mucociliary clearance, which can reduce drug retention. To address these limitations, modified nanoparticles—such as those coated with mucoadhesive or enzyme-resistant materials—are used to improve drug stability and absorption in the nasal cavity.

In neurodegenerative disease applications, Yang et al. developed a multifunctional nanoparticle system for Alzheimer's treatment. Their PEGylated DGL nanoparticles were functionalized with Aleuria aurantia lectin (AAL) for enhanced interaction with olfactory epithelium receptors, facilitating entry through the olfactory route. By codelivering BACE1 siRNA and rapamycin, these nanoparticles successfully reduced amyloid-β accumulation, promoted autophagy, and improved cognitive function in Alzheimer's mouse models. This study

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underscores the potential of intranasal nanoparticle systems in directly targeting neurodegenerative disease mechanisms, offering a safe and effective route for delivering combination therapies.[52] Li et al. investigates the use of lesion-recognizing nanoparticles for nose-to-brain delivery targeting AD. These nanoparticles contain a ROS-responsive polymer core loaded with small interfering RNAs (siRNAs) targeting both the BACE1 enzyme and caspase-3, a known apoptosis marker. When administered intranasally, the delivery of these nanoparticles resulted in significantly higher concentrations in the hippocampus and cortex—areas most affected by Alzheimer's. The nanoparticle concentration in the brain was approximately 3.5 times higher than in other systemic tissues, with a peak retention time of 24 h postadministration. Brain tissue analysis revealed reduced neurodegeneration, with treated mice showing more intact neurons and less neuronal shrinkage in Alzheimer's-affected regions. This indicates that the intranasally delivered nanoparticles not only reached the brain but also produced a tangible protective effect on neuronal structures.[51]

For recent studies in brain cancer treatment, Marrocco and group developed a ferritin-based, stimuli-sensitive nanocarrier with excellent biocompatibility and water solubility, capable of incorporating high concentrations of the potent topoisomerase 1 inhibitor Genz-644282.[55] The nanoparticle-like structure of ferritin allows it to potentially interact with the lipid bilayer of endothelial cells of BBB in a way that aids its transport.[101] This structure, combined with the receptor-mediated endocytosis, helps ferritin to efficiently cross the BBB by interacting with specific receptors such as TfR1 on the surface of endothelial cells that forms the BBB and selectively delivers its payload to gliomas that also express elevated levels of the ferritin/transferrin receptor TfR1 (CD71). Both intranasal and intravenous administration resulted in reduced tumor growth and improved survival rates in glioma-bearing mice. However, intranasal delivery is a simpler and less invasive option that minimizes damage to healthy tissues compared to intravenous methods. These findings could pave the way for a new, safe, and direct ferritin-based drug delivery approach for brain diseases, particularly brain tumors.

Chu et al. successfully used this technique to deliver TMZ-loaded PLGA particles to target GBM in a rodent model.[102] Their study revealed significant cytotoxicity in glioma cells treated with nasal delivery of these modified nanoparticles, as well as improved brain distribution and lower accumulation in other organs compared to intravenous delivery after 4 h. While these promising rodent studies are encouraging,[103,104] further research is needed to determine if these findings will translate into successful human clinical trials. Nonetheless, nose-to-brain delivery holds potential as a powerful technique for minimally invasive brain tumor therapeutics.

In conclusion, intranasal administration leverages the olfactory and trigeminal pathways to bypass the BBB, enabling direct delivery of therapeutic nanoparticles to the brain. This noninvasive route minimizes systemic exposure and improves drug concentration in targeted brain regions. For neurodegenerative diseases, such as Alzheimer's, multifunctional nanoparticles delivered intranasally have shown success in reducing amyloid-β accumulation and improving cognitive outcomes. In brain cancer, specifically GBM, intranasal delivery of drug-loaded nanoparticles has demonstrated enhanced brain targeting and retention compared to traditional intravenous methods. Although promising, this delivery method faces challenges, including mucociliary clearance and enzymatic degradation, which future research should address to maximize therapeutic potential.[105] This can be mitigated by modifying nanoparticles to make them more resistant to enzymatic degradation and mucoadhesive coatings to extend retention time. Modification strategies, such as using mucoadhesive polymers or enzyme-resistant nanoparticles (e.g., PEGylation), can help overcome nasal degradation and improve brain retention. While intranasal delivery can be highly effective for some compounds, the amount of drug reaching the brain may be lower compared to more direct methods like FUS or intravenous delivery. Intranasal administration is well-suited for drugs that are small, lipophilic, and stable in the nasal cavity. It is particularly advantageous for neurodegenerative diseases, like Alzheimer's, where the goal is to deliver agents targeting amyloid-β plaques or tau aggregation.

3.3.3. Magnetic-Guided Nanoparticle Delivery. Although intranasal drug delivery offers a noninvasive and efficient way to bypass the BBB via olfactory and trigeminal nerve pathways, it relies primarily on passive diffusion and neural transport, which can limit precise drug localization. Additionally, factors like mucociliary clearance and enzymatic degradation may reduce its effectiveness over time. In contrast, magnetic nanoparticle (MNP) systems utilize external magnetic fields to actively guide drug-loaded nanoparticles to specific brain regions, offering greater control over drug distribution and enhanced accumulation at target sites. Unlike intranasal delivery, which is well-suited for small molecules and biologics, MNPs excel in localized treatments where precise drug positioning within the brain is required, such as in GBM therapy.

Additionally, MNPs offer a sophisticated method for directing drug-loaded nanoparticles to specific brain regions using external magnetic fields. In a study by Hoshiar et al., MNPs were designed to cross the BBB and reach deep brain regions, such as the hippocampus, by applying an external electromagnetic force. The study demonstrated that nanoparticle size and the magnetic field intensity are critical factors in controlling the movement of nanoparticles through the brain's vascular system. The magnetic gradient used in their experiments was determined by actuator currents ranging from 0.5 to 3 A, resulting in corresponding magnetic field intensities that influenced nanoparticle's aggregation size and steering. The external magnetic fields exert force on the MNPs, steering them toward target brain areas while enhancing their ability to penetrate the BBB. Once guided to the desired region, these nanoparticles can deliver therapeutic agents directly to areas of interest, such as the hippocampus, a key region involved in AD.[50] A study published this year explored the use of chitosan-coated nanoparticles whereby DOX was adsorbed to the magnetic graphene oxide surface for dual active/magnetic targeted drug delivery to glioma. An 1800 G magnet was used to guide the nanoparticles to the tumor site in an in vivo mouse model. Intravenous infusion of NPs displayed significant accumulation in the tumor, inhibition of tumor growth and improved survival in U87MG orthotopic cancer mice model.[43] Additionally, using a magnetic field during treatment further enhanced these outcomes by ensuring targeted delivery of DOX to the brain. Overall, this drug delivery strategy shows promise for effectively treating GBM with minimal side effects. While this method offers precise targeting, one challenge is optimizing the magnetic field strength and duration to ensure efficient nanoparticle accumulation without causing off-target effects. Further research is needed to refine the magnetic field

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parameters and nanoparticle design to ensure safety and efficacy in clinical applications.

The reviewed studies demonstrate significant variability in BBB penetration efficiency across different nanoparticle systems, delivery methods, and experimental models. Intranasal delivery generally achieved higher penetration rates, with efficiencies ranging from 27% to 47% in disease models, compared to intravenous delivery, which was often less than 10% unless aided by auxiliary techniques.[53,55] For instance, ferritin-based nanocarriers reached 13.7% brain accumulation via intranasal administration, while DOX-loaded PLGA nanoparticles delivered intravenously achieved only 5.2% in GBM models and less than 1% in healthy models.[54,55] Ultrasound-assisted delivery improved BBB penetration to 42%, highlighting the role of temporary BBB disruption.[47]

Nonetheless, effective targeting requires careful control of magnetic field strength, duration, and particle properties. If not properly optimized, the magnetic field could fail to guide the particles effectively or cause side effects. It also requires the use of magnets or electromagnetic devices, which might not be easily accessible or scalable for widespread clinical use. The nanoparticles themselves must be designed to interact effectively with the magnetic field and avoid aggregation, which can complicate formulation and efficacy. Magnetic nanoparticle delivery is ideal for drugs that need to be targeted to specific, deep brain regions, such as gliomas or other brain tumors. Drugs like chemotherapy agents (e.g., DOX) or genetic therapies (e.g., siRNA) benefit from magnetic targeting. Modification strategies should focus on optimizing the magnetic properties of nanoparticles and ensuring their stability in the bloodstream to avoid premature aggregation.

4. CURRENT CHALLENGES AND FUTURE PERSPECTIVE

The use of polymeric nanoparticles in overcoming the BBB for neurological disorders has demonstrated significant advancements, offering versatile drug delivery platforms with improved biocompatibility, biodegradability, and targeted delivery capabilities. Among the strategies discussed, PLGA-based nanoparticles are the most extensively studied and have shown the most promise due to their ease of synthesis, sustained drug release, and successful application in both neurodegenerative diseases and brain cancers. Dopamine and chitosan-based polymers also exhibit notable advantages in targeting specific brain regions and enhancing BBB penetration. PEGylation emerges as an essential modification strategy, improving the circulation time and reducing immune recognition of nanoparticles, making it suitable across different neurological conditions. Similarly, receptor-mediated targeting approaches such as TfR-targeted nanoparticles show promise in enhancing drug delivery to both cancerous and degenerative brain tissues. Key factors influencing efficiency included nanoparticle size (optimal at 10−150 nm), charge (positive or slightly neutral for enhanced adhesion), surface modifications (targeting ligands), and disease state, with compromised BBB models consistently showing higher delivery rates. This variability underscores the need for standardized methods to enhance reproducibility and translation to clinical settings.

However, despite these successes, challenges remain. The primary limitation is the inconsistent efficiency of BBB penetration across various models, exacerbated by differences in disease states and individual variability in BBB integrity. Additionally, the risk of neurotoxicity, as well as the rapid clearance of nanoparticles via the immune system, poses significant obstacles. Receptor saturation during prolonged treatment and potential immune responses to repeated doses also limit the efficacy of receptor-targeted strategies.

To address these challenges, future research should focus on optimizing nanoparticle design to enhance both BBB penetration and drug retention in the brain. Multifunctional nanoparticles, which combine various strategies such as receptor targeting with stimuli-responsive elements (pH and ROS), could enhance targeting specificity and controlled drug release. Moreover, tailoring the size and charge of nanoparticles can optimize their interaction with endothelial cells, improving BBB transport efficiency. Further work on reducing immune clearance through enhanced PEGylation or other stealth modifications will help prolong circulation times and ensure sufficient drug delivery.

Moreover, combination therapy holds great potential for future developments. By coencapsulating multiple drugs or therapeutic agents (e.g., chemotherapeutics with neuroprotective agents) within a single nanoparticle system, combination therapy can target different aspects of neurological diseases simultaneously. For instance, combining chemotherapy for GBM with agents that reduce oxidative stress or inflammation could address both tumor growth and the surrounding neuroinflammatory environment, leading to improved outcomes. Nanoparticles designed for combination therapy can also integrate gene silencing techniques, such as siRNA, along with traditional drugs, offering a synergistic effect in conditions like AD and brain cancer.

Noninvasive delivery methods, such as intranasal administration and ultrasound-guided nanoparticle delivery, are particularly promising for combination therapy. These approaches enable localized and controlled delivery of multiple therapeutic agents, reducing systemic side effects and improving patient outcomes. Integrating advanced imaging technologies with these therapies could further enhance real-time monitoring, enabling adjustments to the treatment based on patient-specific needs.

The production of polymeric nanoparticles for clinical use is costly due to material expenses, purification processes, and regulatory compliance requirements. According to Tehrani et al.,[106] the purification of polymeric nanoparticles alone accounts for 30−50% of total production costs, with scale-up complications adding further expenses (Tehrani et al., 2023). Additionally, Cunha et al.[107] highlight that the average cost of producing PLGA-based nanoparticles for neurodegenerative applications is around $1000−5000/g, making it challenging to achieve widespread adoption. To address this, microfluidic synthesis has been proposed as a cost-saving approach, reducing production costs by up to 40% compared to conventional bulk mixing.[108] Continuous manufacturing techniques can also increase batch consistency and reduce waste, helping lower overall production costs.

Regulatory approval remains a major challenge, particularly due to the lack of standardized testing protocols for polymeric nanoparticles. According to Zhang,[109] more than 500 nanoparticle-related clinical trials are currently registered, but only a small fraction (under 10%) progress beyond early phase studies due to regulatory constraints. One key concern is long-term toxicity and biodistribution. Studies have shown that polymeric nanoparticles accumulate in the liver, spleen, and kidneys after prolonged administration, raising concerns about systemic toxicity.[110] Additionally, Guan et al.[111] emphasize that nano-

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particle-based therapies must undergo extensive pharmacokinetic and toxicology studies, which can take 5−10 years before regulatory approval. To overcome these barriers, better in vitro models of the BBB are being developed, with human-derived BBB-on-a-chip models improving predictive accuracy by over 70% compared to animal models.[112] Regulatory agencies are also working toward harmonized guidelines for nanoparticle characterization, which could reduce approval delays.

One of the key challenges in advancing nanoparticle-based drug delivery across the BBB is the lack of standardized evaluation methods for BBB penetration efficiency. Different studies use varying experimental conditions, including in vitro models (e.g., BBB cell culture models), ex vivo techniques (e.g., isolated brain perfusion), and in vivo methods (e.g., animal models like rodents or primates), making direct comparisons difficult. Variations in nanoparticle size, surface charge, coating materials, and administration routes (intravenous, intranasal, or ultrasound-mediated delivery) further complicate reproducibility. Additionally, quantification techniques such as fluorescence tracking, radiolabeling, and mass spectrometry-based biodistribution analysis yield different sensitivity levels, leading to discrepancies in reported penetration efficiencies. To improve translational potential, the field requires standardized protocols for BBB permeability studies, including harmonized nanoparticle characterization methods (e.g., dynamic light scattering, ζ-potential analysis), common in vitro BBB models with reproducible permeability assays, and validated in vivo imaging techniques. Establishing a unified framework for evaluating BBB penetration efficiency across different nanoparticle platforms will enhance comparability between studies, accelerate regulatory approval processes, and facilitate the development of clinically viable brain-targeted therapies.

Scaling up polymeric nanoparticle production is another significant hurdle. Traditional batch processing often leads to batch-to-batch variability of 15−25%, affecting reproducibility.[113] Additionally, nanoparticle encapsulation efficiency drops by 10−20% when moving from small-scale to large-scale production, leading to drug wastage and increased costs. AI-driven optimization of synthesis parameters has been proposed as a way to improve scalability. Seegobin et al.[114] demonstrated that machine learning models could increase PLGA nanoparticle yield while reducing variability, making large-scale production more feasible. Another promising approach is continuous flow manufacturing, which allows for 24-h nanoparticle production with up to 80% higher consistency compared to traditional batch processing.[115] This method has already been implemented in mRNA-lipid nanoparticle vaccine production, demonstrating its feasibility for broader nanoparticle applications.

Future efforts should focus on integrating personalized nanomedicine approaches, such as tailoring nanoparticle coatings to patient-specific BBB transport mechanisms, and developing biodegradable, biosafe polymeric carriers to minimize long-term toxicity risks. Advancements in nanoparticle engineering, regulatory harmonization, and AI-assisted manufacturing will be crucial to overcoming these barriers and ensuring the widespread clinical adoption of polymeric nanoparticles for neurodegenerative disease treatment.

Finally, clinical translation remains a critical goal. No early phase clinical trials (Phase I/II) have been reported to date involving PEGylated PLGA-rivastigmine systems, highlighting a critical gap between laboratory findings and human application. This gap underscores the need for translational studies that assess long-term safety, pharmacokinetics, and large-scale production feasibility.

5. CONCLUSION

Overall, polymeric nanoparticles hold transformative potential in overcoming the BBB for the treatment of neurodegenerative diseases and brain cancers. Among these, PLGA-based systems remain the most clinically advanced due to their great biocompatibility, sustained drug release, and versatility in surface modification. Functional strategies such as PEGylation, receptor-mediated targeting, and stimuli-responsive release have further improved targeting efficiency and therapeutic precision. In parallel, noninvasive delivery techniques—particularly intranasal administration and ultrasound-guided approaches—are enhancing localized delivery while reducing systemic side effects. Despite substantial preclinical success, the translation of these systems into clinical use is still constrained by several key challenges. These include limited standardization of BBB models, immune-related toxicity, production scalability, and stringent regulatory requirements. Innovative solutions such as multifunctional nanoparticles, combination therapy platforms, continuous manufacturing, and AI-assisted optimization are beginning to address these barriers. However, a critical gap remains in early phase clinical testing—underscoring the need for harmonized evaluation protocols and deeper translational research. With continued interdisciplinary collaboration and regulatory innovation, polymeric nanoparticles are poised to play a central role in the next generation of CNS therapeutics.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Zhang, W.; Mehta, A.; Tong, Z.; Esser, L.; Voelcker, N. H. Development of Polymeric Nanoparticles for Blood-Brain Barrier Transfer-Strategies and Challenges. *Adv. Sci. (Weinh)* **2021**, *8*, 2003937.

(2) Organization, W. H. *Over 1 in 3 people affected by neurological conditions, the leading cause of illness and disability worldwide*; 2024. https://www.who.int/news/item/14-03-2024-over-1-in-3-people-affected-by-neurological-conditions--the-leading-cause-of-illness-and-disability-worldwide.

(3) Steinmetz, J. D.; et al. Global, regional, and national burden of disorders affecting the nervous system, 1990−2021: a systematic analysis for the Global Burden of Disease Study. *Lancet Neurology* **2024**, *23*, 344−381.

(4) Dugger, B. N.; Dickson, D. W. Pathology of neurodegenerative diseases. *Cold Spring Harbor perspectives in biology* **2017**, *9*, a028035.

(5) Zhang, J.; Darley-Usmar, V. Mitochondrial dysfunction in neurodegenerative disease: Protein aggregation, autophagy, and oxidative stress. *Mitochondrial dysfunction in neurodegenerative disorders*; Springer: London, 2012; Vols. *95*−*111*.

(6) Shastry, B. S. Neurodegenerative disorders of protein aggregation. *Neurochemistry international* **2003**, *43*, 1−7.

(7) Lin, M. T.; Beal, M. F. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* **2006**, *443*, 787−795.

(8) Zeevalk, G.; Bernard, L.; Song, C.; Gluck, M.; Ehrhart, J. Mitochondrial inhibition and oxidative stress: reciprocating players in neurodegeneration. *Antioxidants & redox signaling* **2005**, *7*, 1117−1139.

(9) Rodolfo, C.; Ciccosanti, F.; Giacomo, G. D.; Piacentini, M.; Fimia, G. M. Proteomic analysis of mitochondrial dysfunction in neurodegenerative diseases. *Expert Rev. Proteomics* **2010**, *7*, 519−542.

(10) Moonshi, S. S.; et al. A comparison of PET imaging agents for the assessment of therapy efficacy in a rodent model of glioma. *Am. J. Nucl. Med. Mol. Imaging* **2013**, *3*, 397−407.

(11) Alves, T. R.; et al. Glioblastoma cells: A heterogeneous and fatal tumor interacting with the parenchyma. *Life Sciences* **2011**, *89*, 532−539.

(12) Ananda, S.; et al. Phase 2 trial of Temozolomide and pegylated liposomal doxorubicin in the treatment of patients with glioblastoma multiforme following concurrent radiotherapy and chemotherapy. *Journal of Clinical Neuroscience* **2011**, *18*, 1444−1448.

(13) Zhang, W.; Mehta, A.; Tong, Z.; Esser, L.; Voelcker, N. H. Development of Polymeric Nanoparticles for Blood−Brain Barrier Transfer—Strategies and Challenges. *Advanced Science* **2021**, *8*, 2003937.

(14) Nance, E.; et al. Non-invasive delivery of stealth, brain-penetrating nanoparticles across the blood−brain barrier using MRI-guided focused ultrasound. *J. Controlled Release* **2014**, *189*, 123−132.

(15) Khan, A. R.; Yang, X.; Fu, M.; Zhai, G. Recent progress of drug nanoformulations targeting to brain. *J. Controlled Release* **2018**, *291*, 37−64.

(16) Zhou, Y.; Peng, Z.; Seven, E. S.; Leblanc, R. M. Crossing the blood-brain barrier with nanoparticles. *Journal of controlled release* **2018**, *270*, 290−303.

(17) Pardridge, W. M. Treatment of Alzheimer's Disease and Blood−Brain Barrier Drug Delivery. *Pharmaceuticals* **2020**, *13*, 394.

(18) Mitchell, R. W.; Hatch, G. M. Fatty acid transport into the brain: Of fatty acid fables and lipid tails. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)* **2011**, *85*, 293−302.

(19) Hanske, S.; Dyrna, F.; Bechmann, I.; Krueger, M. Different segments of the cerebral vasculature reveal specific endothelial specifications, while tight junction proteins appear equally distributed. *Brain Structure and Function* **2017**, *222*, 1179−1192.

(20) Engelhardt, B. Development of the blood-brain barrier. *Cell Tissue Res.* **2003**, *314*, 119−129.

(21) Tilling, T.; et al. Expression and adhesive properties of basement membrane proteins in cerebral capillary endothelial cell cultures. *Cell Tissue Res.* **2002**, *310*, 19−29.

(22) Zapata-Acevedo, J. F.; et al. Laminin as a Biomarker of Blood−Brain Barrier Disruption under Neuroinflammation: A Systematic Review. *International Journal of Molecular Sciences* **2022**, *23*, 6788.

(23) Kawoos, U.; Abutarboush, R.; Gu, M.; Chen, Y.; Statz, J. K.; Goodrich, S. Y.; Ahlers, S. T. Blast-induced temporal alterations in blood−brain barrier properties in a rodent model. *Sci. Rep.* **2021**, *11*, 5906.

(24) Candelario-Jalil, E.; Dijkhuizen, R. M.; Magnus, T. Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. *Stroke* **2022**, *53*, 1473−1486.

(25) Mainprize, T.; et al. Blood-Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study. *Sci. Rep.* **2019**, *9*, 321.

(26) Harati, R.; et al. miR-27a-3p regulates expression of intercellular junctions at the brain endothelium and controls the endothelial barrier permeability. *PLoS One* **2022**, *17*, No. e0262152.

(27) Qosa, H.; Miller, D. S.; Pasinelli, P.; Trotti, D. Regulation of ABC efflux transporters at blood-brain barrier in health and neurological disorders. *Brain Res.* **2015**, *1628*, 298−316.

(28) Haorah, J.; et al. Oxidative stress activates protein tyrosine kinase and matrix metalloproteinases leading to blood−brain barrier dysfunction. *Journal of Neurochemistry* **2007**, *101*, 566−576.

(29) Chen, Y.; Dalwadi, G.; Benson, H. Drug delivery across the blood-brain barrier. *Curr. Drug Delivery* **2004**, *1*, 361−376.

(30) Tamai, I.; Tsuji, A. Transporter-Mediated Permeation of Drugs Across the Blood−Brain Barrier. *J. Pharm. Sci.* **2000**, *89*, 1371−1388.

(31) Fortin, D.; McCormick, C. I.; Remsen, L. G.; Nixon, R.; Neuwelt, E. A. Unexpected Neurotoxicity of Etoposide Phosphate Administered in Combination with Other Chemotherapeutic Agents after Blood-Brain Barrier Modification to Enhance Delivery, Using Propofol for General Anesthesia, in a Rat Model. *Neurosurgery* **2000**, *47*, 199.

(32) Deo, A. K.; Theil, F.-P.; Nicolas, J.-M. Confounding Parameters in Preclinical Assessment of Blood−Brain Barrier Permeation: An Overview With Emphasis on Species Differences and Effect of Disease States. *Mol. Pharmaceutics* **2013**, *10*, 1581−1595.

(33) Groothuis, D. R. The blood-brain and blood-tumor barriers: A review of strategies for increasing drug delivery. *Neuro-Oncology* **2000**, *2*, 45−59.

(34) Tam, V. H.; Sosa, C.; Liu, R.; Yao, N.; Priestley, R. D. Nanomedicine as a non-invasive strategy for drug delivery across the blood brain barrier. *Int. J. Pharm.* **2016**, *515*, 331−342.

(35) Tsou, Y.-H.; Zhang, X.-Q.; Zhu, H.; Syed, S.; Xu, X. Drug Delivery to the Brain across the Blood−Brain Barrier Using Nanomaterials. *Small* **2017**, *13*, 1701921.

(36) Mulvihill, J. J.; et al. Drug delivery across the blood−brain barrier: recent advances in the use of nanocarriers. *Nanomedicine* **2020**, *15*, 205−214.

(37) Sharma, G.; et al. Advances in nanocarriers enabled brain targeted drug delivery across blood brain barrier. *Int. J. Pharm.* **2019**, *559*, 360−372.

(38) Agrawal, P.; et al. TPGS-chitosan cross-linked targeted nanoparticles for effective brain cancer therapy. *Materials Science and Engineering: C* **2017**, *74*, 167−176.

(39) Caban-Toktas, S.; et al. Combination of Paclitaxel and R-flurbiprofen loaded PLGA nanoparticles suppresses glioblastoma growth on systemic administration. *Int. J. Pharm.* **2020**, *578*, 119076.

(40) Turabee, M. H.; Jeong, T. H.; Ramalingam, P.; Kang, J. H.; Ko, Y. T. N,N,N-trimethyl chitosan embedded in situ Pluronic F127 hydrogel for the treatment of brain tumor. *Carbohydr. Polym.* **2019**, *203*, 302−309.

(41) Agarwal, S.; Mohamed, M. S.; Mizuki, T.; Maekawa, T.; Sakthi Kumar, D. Chlorotoxin modified morusin−PLGA nanoparticles for targeted glioblastoma therapy. *J. Mater. Chem. B* **2019**, *7*, 5896−5919.

(42) Ahmad, S.; et al. Brain targeted delivery of carmustine using chitosan coated nanoparticles via nasal route for glioblastoma treatment. *Int. J. Biol. Macromol.* **2022**, *221*, 435−445.

(43) Dash, B. S.; Lu, Y.-J.; Huang, Y.-S.; Chen, J.-P. Chitosan-coated magnetic graphene oxide for targeted delivery of doxorubicin as a

https://doi.org/10.1021/acsabm.4c01956
ACS Appl. Bio Mater. 2025, 8, 4416−4431

nanomedicine approach to treat glioblastoma. *Int. J. Biol. Macromol.* **2024**, *260*, 129401.
(44) Zhang, L.; Fan, J.; Li, G.; Yin, Z.; Fu, B. M. Transcellular Model for Neutral and Charged Nanoparticles Across an In Vitro Blood−Brain Barrier. *Cardiovascular Engineering and Technology* **2020**, *11*, 607−620.
(45) Cai, L.; et al. Endo/Lysosome-Escapable Delivery Depot for Improving BBB Transcytosis and Neuron Targeted Therapy of Alzheimer's Disease. *Adv. Funct. Mater.* **2020**, *30*, 1909999.
(46) Darwish, W. M.; Bayoumi, N. A.; Ebeid, N. H. Biocompatible mucoadhesive nanoparticles for brain targeting of ropinirole hydrochloride: Formulations, radiolabeling and biodistribution. *Biopolymers* **2022**, *113*, No. e23489.
(47) Liu, Y.; et al. Microbubbles in combination with focused ultrasound for the delivery of quercetin-modified sulfur nanoparticles through the blood brain barrier into the brain parenchyma and relief of endoplasmic reticulum stress to treat Alzheimer's disease. *Nanoscale* **2020**, *12*, 6498−6511.
(48) Yuan, X.; et al. A diselenide bond-containing ROS-responsive ruthenium nanoplatform delivers nerve growth factor for Alzheimer's disease management by repairing and promoting neuron regeneration. *J. Mater. Chem. B* **2021**, *9*, 7835−7847.
(49) Xu, R.; Wang, J.; Xu, J.; Song, X.; Huang, H.; Feng, Y.; Fu, C. Rhynchophylline loaded-mPEG-PLGA nanoparticles coated with tween-80 for preliminary study in Alzheimer's disease. *Int. J. Nanomed.* **2020**, *15*, 1149.
(50) Kafash Hoshiar, A.; Dadras Javan, S.; Le, T.-A.; Hairi Yazdi, M. R.; Yoon, J. Studies on Aggregated Nanoparticles Steering during Deep Brain Membrane Crossing. *Nanomaterials* **2021**, *11*, 2754.
(51) Li, J.; et al. Enhanced Nose-to-Brain Delivery of Combined Small Interfering RNAs Using Lesion-Recognizing Nanoparticles for the Synergistic Therapy of Alzheimer's Disease. *ACS Appl. Mater. Interfaces* **2023**, *15*, 53177−53188.
(52) Yang, X.; et al. Intranasal Delivery of BACE1 siRNA and Rapamycin by Dual Targets Modified Nanoparticles for Alzheimer's Disease Therapy. *Small* **2022**, *18*, 2203182.
(53) Mohebichamkhorami, F.; et al. Microfluidic Synthesis of Ultrasmall Chitosan/Graphene Quantum Dots Particles for Intranasal Delivery in Alzheimer's Disease Treatment. *Small* **2023**, *19*, 2207626.
(54) Maksimenko, O.; et al. Doxorubicin-loaded PLGA nanoparticles for the chemotherapy of glioblastoma: Towards the pharmaceutical development. *Int. J. Pharm.* **2019**, *572*, 118733.
(55) Marrocco, F.; et al. Nose-to-brain selective drug delivery to glioma via ferritin-based nanovectors reduces tumor growth and improves survival rate. *Cell Death & Disease* **2024**, *15*, 262.
(56) Rabanel, J.-M.; Piec, P.-A.; Landri, S.; Patten, S. A.; Ramassamy, C. Transport of PEGylated-PLA nanoparticles across a blood brain barrier model, entry into neuronal cells and in vivo brain bioavailability. *J. Controlled Release* **2020**, *328*, 679−695.
(57) Tripathi, S. K.; et al. Donepezil loaded PLGA Nanoparticles, from Modified Nano-Precipitation, an Advanced Drug Delivery System to treat Alzheimer Disease. *Journal of Physics: Conference Series* **2021**, *1849*, 012001.
(58) Pahuja, R.; et al. Trans-Blood Brain Barrier Delivery of Dopamine-Loaded Nanoparticles Reverses Functional Deficits in Parkinsonian Rats. *ACS Nano* **2015**, *9*, 4850−4871.
(59) Trapani, A.; et al. Novel Nanoparticles Based on N,O-Carboxymethyl Chitosan-Dopamine Amide Conjugate for Nose-to-Brain Delivery. *Pharmaceutics* **2022**, *14*, 147.
(60) Gao, Y.; et al. NIR-Assisted MgO-Based Polydopamine Nanoparticles for Targeted Treatment of Parkinson's Disease through the Blood-Brain Barrier. *Adv. Healthc Mater.* **2022**, *11*, No. e2201655.
(61) Ortega Martínez, E.; Morales Hernández, M. E.; Castillo-González, J.; González-Rey, E.; Ruiz Martínez, M. A. Dopamine-loaded chitosan-coated solid lipid nanoparticles as a promise nanocarriers to the CNS. *Neuropharmacology* **2024**, *249*, 109871.
(62) Battaglini, M.; et al. Polydopamine Nanoparticles as an Organic and Biodegradable Multitasking Tool for Neuroprotection and Remote Neuronal Stimulation. *ACS Appl. Mater. Interfaces* **2020**, *12*, 35782−35798.
(63) Huang, Q.; Jiang, C.; Xia, X.; Wang, Y.; Yan, C.; Wang, X.; Lei, T.; Yang, X.; Yang, W.; Cheng, G.; Gao, H. Pathological BBB Crossing Melanin-Like Nanoparticles as Metal-Ion Chelators and Neuroinflammation Regulators against Alzheimer's Disease. *Research* **2023**, *6*, 0180.
(64) Zhi, K.; et al. PLGA Nanoparticle-Based Formulations to Cross the Blood−Brain Barrier for Drug Delivery: From R&D to cGMP. *Pharmaceutics* **2021**, *13*, 500.
(65) Spindler, L. M.; et al. Nano-in-Micro-Particles Consisting of PLGA Nanoparticles Embedded in Chitosan Microparticles via Spray-Drying Enhances Their Uptake in the Olfactory Mucosa. *Front. Pharmacol.* **2021**, *12*. DOI: 10.3389/fphar.2021.732954.
(66) Mahanta, A. K.; Chaulagain, B.; Trivedi, R.; Singh, J. Mannose-Functionalized Chitosan-Coated PLGA Nanoparticles for Brain-Targeted Codelivery of CBD and BDNF for the Treatment of Alzheimer's Disease. *ACS Chem. Neurosci.* **2024**, *15*, 4021−4032.
(67) Moonshi, S. S.; et al. Spiky Silver−Iron Oxide Nanohybrid for Effective Dual-Imaging and Synergistic Thermo-Chemotherapy. *ACS Appl. Mater. Interfaces* **2023**, *15*, 42153.
(68) Papi, M.; et al. Clinically approved PEGylated nanoparticles are covered by a protein corona that boosts the uptake by cancer cells. *Nanoscale* **2017**, *9*, 10327−10334.
(69) Pozzi, D.; et al. Effect of polyethyleneglycol (PEG) chain length on the bio−nano-interactions between PEGylated lipid nanoparticles and biological fluids: from nanostructure to uptake in cancer cells. *Nanoscale* **2014**, *6*, 2782−2792.
(70) Suk, J. S.; Xu, Q.; Kim, N.; Hanes, J.; Ensign, L. M. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv. Drug Deliv Rev.* **2016**, *99*, 28−51.
(71) Tang, J. L.; et al. A methotrexate labelled dual metal oxide nanocomposite for long-lasting anti-cancer theranostics. *Materials Today Bio* **2025**, *30*, 101377.
(72) Wu, Y.; et al. Engineering chitosan nano-cocktail containing iron oxide and ceria: a two-in-one approach for treatment of inflammatory diseases and tracking of material delivery. *Materials Science and Engineering: C* **2021**, *131*, 112477.
(73) Wu, Y.; et al. Chitosan nanococktails containing both ceria and superparamagnetic iron oxide nanoparticles for reactive oxygen species-related theranostics. *ACS Applied Nano Materials* **2021**, *4*, 3604−3618.
(74) Ta, H. T.; Dass, C. R.; Larson, I.; Choong, P. F.; Dunstan, D. E. A chitosan hydrogel delivery system for osteosarcoma gene therapy with pigment epithelium-derived factor combined with chemotherapy. *Biomaterials* **2009**, *30*, 4815−4823.
(75) Ta, H. T.; Dass, C. R.; Larson, I.; Choong, P. F.; Dunstan, D. E. A chitosan−dipotassium orthophosphate hydrogel for the delivery of doxorubicin in the treatment of osteosarcoma. *Biomaterials* **2009**, *30*, 3605−3613.
(76) Ta, H. T.; Han, H.; Larson, I.; Dass, C. R.; Dunstan, D. E. Chitosan-dibasic orthophosphate hydrogel: A potential drug delivery system. *International journal of pharmaceutics* **2009**, *371*, 134−141.
(77) Ta, H. T.; Dass, C. R.; Dunstan, D. E. Injectable chitosan hydrogels for localised cancer therapy. *J. Controlled Release* **2008**, *126*, 205−216.
(78) Mahanta, A. K.; Chaulagain, B.; Trivedi, R.; Singh, J. Mannose-Functionalized Chitosan-Coated PLGA Nanoparticles for Brain-Targeted Codelivery of CBD and BDNF for the Treatment of Alzheimer's Disease. *ACS Chem. Neurosci.* **2024**, *15*, 4021−4032.
(79) Cortés, H. A Reevaluation of Chitosan-Decorated Nanoparticles to Cross the Blood-Brain Barrier. *Membranes (Basel)* **2020**, *10*, 212.
(80) Vllasaliu, D.; et al. Tight junction modulation by chitosan nanoparticles: comparison with chitosan solution. *Int. J. Pharm.* **2010**, *400*, 183−193.
(81) van der Lubben, I. M.; Verhoef, J. C.; Borchard, G.; Junginger, H. E. Chitosan and its derivatives in mucosal drug and vaccine delivery. *Eur. J. Pharm. Sci.* **2001**, *14*, 201−207.
(82) Lu, B.; Lv, X.; Le, Y. Chitosan-Modified PLGA Nanoparticles for Control-Released Drug Delivery. *Polymers (Basel)* **2019**, *11*, 304.
(83) Ramalho, M. J.; Serra, É.; Lima, J.; Loureiro, J. A.; Pereira, M. C. Chitosan-PLGA mucoadhesive nanoparticles for gemcitabine repur-

posing for glioblastoma therapy. *Eur. J. Pharm. Biopharm.* **2024**, *200*, 114326.
(84) Caprifico, A. E.; Foot, P. J. S.; Polycarpou, E.; Calabrese, G. Overcoming the Blood-Brain Barrier: Functionalised Chitosan Nanocarriers. *Pharmaceutics* **2020**, *12*, 1013.
(85) Ramalho, M. J.; et al. Receptor-mediated PLGA nanoparticles for glioblastoma multiforme treatment. *Int. J. Pharm.* **2018**, *545*, 84−92.
(86) Jokar, S.; et al. Synthesis, biological evaluation and preclinical study of a novel 99mTc-peptide: A targeting probe of amyloid-β plaques as a possible diagnostic agent for Alzheimer's disease. *Bioorganic Chemistry* **2020**, *99*, 103857.
(87) Zhang, Y.; et al. Mitochondria-targeted nanoparticles in treatment of neurodegenerative diseases. *Exploration* **2021**, *1*, 20210115.
(88) Liu, Y.; et al. Suppressing Nanoparticle-Mononuclear Phagocyte System Interactions of Two-Dimensional Gold Nanorings for Improved Tumor Accumulation and Photothermal Ablation of Tumors. *ACS Nano* **2017**, *11*, 10539−10548.
(89) dos Santos, S. N.; et al. Avoiding the mononuclear phagocyte system using human albumin for mesoporous silica nanoparticle system. *Microporous Mesoporous Mater.* **2017**, *251*, 181−189.
(90) Schaeublin, N. M.; et al. Surface charge of gold nanoparticles mediates mechanism of toxicity. *Nanoscale* **2011**, *3*, 410−420.
(91) Fröhlich, E. The role of surface charge in cellular uptake and cytotoxicity of medical nanoparticles. *Int. J. Nanomedicine* **2012**, *7*, 5577−5591.
(92) Betzer, O.; Shilo, M.; Motiei, M.; Popovtzer, R. *Insulin-Coated Gold Nanoparticles As an Effective Approach for Bypassing the Blood-Brain Barrier*; SPIE, 2019; Vol. *10891*.
(93) Nowak, M.; Brown, T. D.; Graham, A.; Helgeson, M. E.; Mitragotri, S. Size, shape, and flexibility influence nanoparticle transport across brain endothelium under flow. *Bioeng Transl Med.* **2020**, *5*, No. e10153.
(94) Da Silva-Candal, A.; et al. Shape effect in active targeting of nanoparticles to inflamed cerebral endothelium under static and flow conditions. *J. Controlled Release* **2019**, *309*, 94−105.
(95) García-Pardo, J.; et al. Bioinspired Theranostic Coordination Polymer Nanoparticles for Intranasal Dopamine Replacement in Parkinson's Disease. *ACS Nano* **2021**, *15*, 8592−8609.
(96) Agrawal, M.; et al. Stimuli-responsive In situ gelling system for nose-to-brain drug delivery. *J. Controlled Release* **2020**, *327*, 235−265.
(97) Chen, K.-T.; Wei, K.-C.; Liu, H.-L. Theranostic strategy of focused ultrasound induced blood-brain barrier opening for CNS disease treatment. *Front. Pharmacol.* **2019**, *10*, 86.
(98) Rezai, A. R.; et al. Focused ultrasound-mediated blood-brain barrier opening in Alzheimer's disease: long-term safety, imaging, and cognitive outcomes. *J. Neurosurg* **2023**, *139*, 275−283.
(99) Idbaih, A.; et al. Safety and Feasibility of Repeated and Transient Blood-Brain Barrier Disruption by Pulsed Ultrasound in Patients with Recurrent Glioblastoma. *Clin. Cancer Res.* **2019**, *25*, 3793−3801.
(100) Meng, Y.; et al. Current Progress in Magnetic Resonance-Guided Focused Ultrasound to Facilitate Drug Delivery across the Blood-Brain Barrier. *Pharmaceutics* **2024**, *16*, 719.
(101) Fan, K.; et al. Ferritin Nanocarrier Traverses the Blood Brain Barrier and Kills Glioma. *ACS Nano* **2018**, *12*, 4105−4115.
(102) Chu, L.; et al. Nose-to-brain delivery of Temozolomide-loaded PLGA nanoparticles functionalized with anti-EPHA3 for glioblastoma targeting. *Drug Deliv* **2018**, *25*, 1634−1641.
(103) Wang, L.; et al. Intranasal Delivery of Temozolomide-Conjugated Gold Nanoparticles Functionalized with Anti-EphA3 for Glioblastoma Targeting. *Mol. Pharmaceutics* **2021**, *18*, 915−927.
(104) Wang, S.; et al. Temozolomide hexadecyl ester targeted plga nanoparticles for drug-resistant glioblastoma therapy via intranasal administration. *Front. Pharmacol.* **2022**, *13*. DOI: 10.3389/fphar.2022.965789.
(105) Gizurarson, S. The effect of cilia and the mucociliary clearance on successful drug delivery. *Biol. Pharm. Bull.* **2015**, *38*, 497−506.
(106) Tehrani, S. F.; Bharadwaj, P.; Leblond Chain, J.; Roullin, V. G. Purification processes of polymeric nanoparticles: How to improve their clinical translation? *J. Controlled Release* **2023**, *360*, 591−612.
(107) Cunha, A.; Gaubert, A.; Latxague, L.; Dehay, B. PLGA-Based Nanoparticles for Neuroprotective Drug Delivery in Neurodegenerative Diseases. *Pharmaceutics* **2021**, *13*, 1042.
(108) Jacobs, E.; et al. Design and scale-up of amorphous drug nanoparticles production via a one-step anhydrous continuous process. *Int. J. Pharm.* **2022**, *628*, 122304.
(109) Zhang, N. Promoting the bench-to-bedside translation of nanomedicines. *Med. Rev.* **2023**, *3*, 1−3.
(110) Haidar, L. L.; Bilek, M.; Akhavan, B. Surface Bio-engineered Polymeric Nanoparticles. *Small* **2024**, *20*, No. e2310876.
(111) Csóka, I.; Ismail, R.; Jójárt-Laczkovich, O.; Pallagi, E. Regulatory Considerations, Challenges and Risk-based Approach in Nanomedicine Development. *Curr. Med. Chem.* **2021**, *28*, 7461−7476.
(112) Pérez-López, A.; Torres-Suárez, A. I.; Martín-Sabroso, C.; Aparicio-Blanco, J. An overview of in vitro 3D models of the blood-brain barrier as a tool to predict the in vivo permeability of nanomedicines. *Adv. Drug Deliv Rev.* **2023**, *196*, 114816.
(113) Operti, M. C. Industrial Scale Manufacturing and Downstream Processing of PLGA-Based Nanomedicines Suitable for Fully Continuous Operation. *Pharmaceutics* **2022**, *14*, 276.
(114) Seegobin, N.; et al. Optimising the production of PLGA nanoparticles by combining design of experiment and machine learning. *Int. J. Pharm.* **2024**, *667*, 124905.
(115) Hengelbrock, A.; Schmidt, A.; Strube, J. Formulation of Nucleic Acids by Encapsulation in Lipid Nanoparticles for Continuous Production of mRNA. *Processes* **2023**, *11*, 1718.

https://doi.org/10.1021/acsabm.4c01956
ACS Appl. Bio Mater. 2025, 8, 4416−4431