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Chapter 5: Polymeric Nanoparticles, Dendrimers, NPs: Versatile Platforms for Sustained Brain Delivery

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Abstract

Polymeric nanoparticles, dendrimers, and nanoparticles (NPs) represent a versatile platform for sustained brain delivery of therapeutic agents. These nanocarriers offer unique advantages in overcoming the blood-brain barrier (BBB) and achieving targeted drug delivery to the central nervous system. Polymeric nanoparticles, composed of biodegradable and biocompatible materials, provide controlled release and enhanced stability of encapsulated drugs. Dendrimers, with their highly branched structure, offer precise control over size, shape, and surface functionality, enabling tailored interactions with biological systems. Various types of NPs, including lipid-based and inorganic nanoparticles, contribute to this diverse arsenal of delivery vehicles. These nanocarriers can be engineered to improve drug solubility, increase circulation time, and facilitate BBB penetration through active targeting mechanisms. Recent advancements in nanocarrier design have focused on enhancing their ability to deliver a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids, for sustained periods. This sustained delivery approach holds promise for treating chronic neurological disorders by maintaining therapeutic drug concentrations in the brain while minimizing systemic exposure and side effects.

Keywords: *Polymeric nanoparticles, Polymeric dendrimer, Targeted drug delivery, Sustained release, Lipid-based nanoparticles.*

1. Introduction

Polymeric nanoparticles, dendrimers, and nanoparticles (NPs) have emerged as promising platforms for sustained brain drug delivery, addressing the challenges posed by the blood-brain barrier (BBB). These advanced drug delivery systems offer unique advantages in terms of size, surface properties, and drug encapsulation capabilities, making them ideal candidates for targeting neurological disorders [1]. Polymeric nanoparticles, typically ranging from 10 to 1000 nm in size, are composed of biodegradable and biocompatible polymers. Their versatility allows for the encapsulation of various therapeutic agents, including small molecules, proteins, and nucleic acids. The polymer matrix provides controlled release of the encapsulated drug, ensuring sustained delivery to the brain over extended periods. Dendrimers, on the other hand, are highly branched, monodisperse macromolecules with a well-defined structure [2, 3]. Their unique architecture allows for precise control over size, shape, and surface functionality. Dendrimers can be tailored to enhance BBB penetration and target specific brain regions, making them valuable tools for treating neurological disorders. Nanoparticles, encompassing a broad range of nanoscale materials, offer diverse possibilities for brain drug delivery [4]. These include inorganic nanoparticles, lipid-based nanocarriers, and hybrid systems as summarized in fig 5.1. Their small size and surface modifications enable them to overcome the BBB and achieve targeted delivery to specific brain areas. The combination of these nanoplatforms provides a versatile toolkit for addressing the complexities of brain drug delivery. By leveraging their unique properties, researchers can develop tailored strategies to enhance drug bioavailability, improve therapeutic efficacy, and minimize side effects in the treatment of neurological disorders [5, 6].

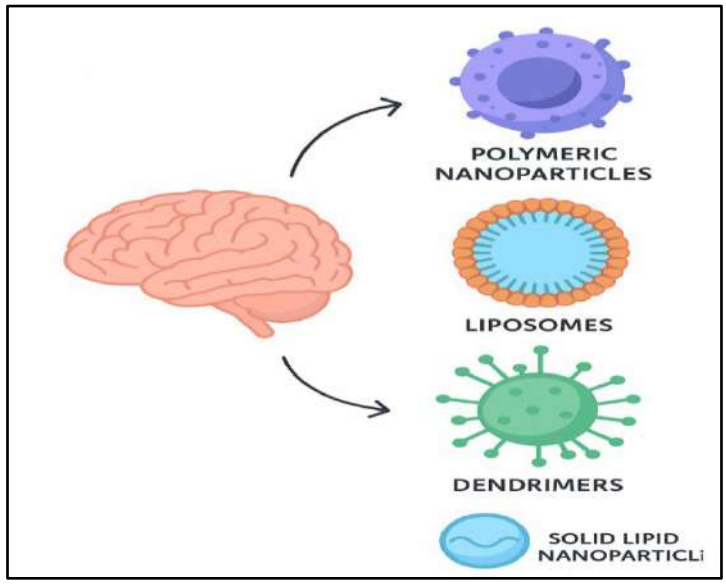

Fig 5.1: Types of Nanocarriers based targeted brain delivery

2. Types of Nanocarriers for Brain Delivery

2.1 Polymeric Nanoparticles

Polymeric nanoparticles are microscopic particles ranging from 10 to 1000 nanometres in size, composed of biodegradable and biocompatible polymers. These nanostructures have gained significant attention in the field of drug delivery due to their versatility and ability to encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids [7, 8]. The unique properties of polymeric nanoparticles make them ideal candidates for various biomedical applications. Their small size allows them to penetrate biological barriers and reach target tissues more effectively than conventional drug formulations as describe in fig 5.1. The polymer matrix provides controlled release of the encapsulated drug, ensuring sustained delivery over extended periods [9]. One of the key advantages of polymeric nanoparticles is their customizable surface properties. Through surface modifications, researchers can enhance the nanoparticles' stability, improve their targeting capabilities, and reduce their recognition by the immune system. This versatility enables the development of tailored drug delivery systems for specific therapeutic applications [10]. Polymeric nanoparticles have shown promise in cancer therapy, where they can be designed to accumulate preferentially in tumour tissues through the enhanced permeability and retention (EPR) effect. They have also been explored for targeted delivery to other organs, such as the brain, by incorporating ligands that facilitate crossing the blood-brain barrier [11]. Furthermore, polymeric nanoparticles offer the potential for co-delivery of multiple therapeutic agents, enabling combination therapies and overcoming drug resistance mechanisms. Their biodegradability ensures that the nanoparticles can be safely eliminated from the body after delivering their payload, reducing the risk of long-term toxicity [12].

2.2 Dendrimers

Dendrimers are highly branched, tree-like macromolecules with a unique architecture that sets them apart from traditional linear polymers. These nanoscale structures consist of a central core from which branching units emanate in a symmetrical and controlled manner [13]. The branching process continues outward, creating successive "generations" of dendrimers with increasing size and number of terminal groups. The synthesis of dendrimers follows two main approaches: divergent and convergent. In the divergent method, growth starts from the core and extends outward, while the convergent approach begins with the outer segments and progresses inward [14]. This precise control over synthesis allows for the creation of dendrimers with well-defined structures, molecular weights, and surface functionalities. Dendrimers possess several unique properties that make them attractive for various applications. Their globular shape and high surface area-to-volume ratio provide numerous sites for drug encapsulation or attachment [15]. The internal cavities can host guest molecules, while the multivalent surface allows for the conjugation of targeting ligands, imaging agents, or therapeutic compounds. In the field of nanomedicine, dendrimers have shown promise

as drug delivery vehicles, gene transfection agents, and contrast agents for medical imaging. Their ability to cross biological barriers and their potential for multifunctionality make them valuable tools in targeted therapy and diagnostics. However, challenges such as potential toxicity and the need for further optimization of their physicochemical properties remain areas of ongoing research [16-18].

2.3 Liposomes

Liposomes are microscopic vesicles composed of one or more lipid bilayers enclosing an aqueous core. These spherical structures mimic biological membranes and have gained significant attention in pharmaceutical and biomedical applications [19]. The lipid bilayer typically consists of phospholipids, which spontaneously arrange themselves with their hydrophilic heads facing the aqueous environments and their hydrophobic tails forming the interior of the bilayer. Liposomes can be classified based on their size and number of bilayers. Unilamellar vesicles contain a single bilayer, while multilamellar vesicles consist of multiple concentric bilayers [20, 21]. The versatility of liposomes lies in their ability to encapsulate both hydrophilic and hydrophobic compounds. Hydrophilic drugs can be entrapped in the aqueous core, while lipophilic molecules can be incorporated into the lipid bilayer. One of the key advantages of liposomes is their biocompatibility and biodegradability [22]. They can be designed to have specific surface properties, charge, and size, allowing for tailored drug delivery applications. Liposomes can enhance the therapeutic index of drugs by improving their solubility, protecting them from degradation, and modifying their pharmacokinetics and biodistribution. In recent years, advanced liposomal formulations have been developed, including stealth liposomes with prolonged circulation times and targeted liposomes that can deliver drugs to specific tissues or cells. These innovations have led to the successful clinical application of liposomal drugs in cancer therapy, antimicrobial treatments, and vaccine delivery [23, 24].

2.4 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal drug delivery systems composed of physiological lipids that remain solid at body temperature. These nanocarriers, typically ranging from 50 to 1000 nm in size, offer a unique alternative to traditional drug delivery systems. SLNs consist of a solid lipid core matrix stabilized by surfactants, which can incorporate lipophilic and hydrophilic drugs [25, 26]. The solid core of SLNs provides several advantages, including enhanced physical stability, protection of incorporated drugs from degradation, and controlled drug release. The lipid matrix can be composed of various biocompatible and biodegradable lipids, such as triglycerides, fatty acids, and waxes. This composition allows for high drug loading capacity and improved bioavailability of poorly water-soluble drugs [27]. SLNs offer versatility in administration routes, including oral, parenteral, and topical applications. They have shown promise in targeted drug delivery, particularly in cancer therapy and brain targeting. The surface of SLNs can be modified with ligands or polymers to enhance their circulation time and targeting efficiency [28]. One of the key advantages of SLNs

is their ability to overcome limitations associated with other nanocarriers, such as stability issues of liposomes and toxicity concerns of polymeric nanoparticles. However, challenges remain, including potential drug expulsion during storage and limited loading capacity for hydrophilic drugs [29].

2.5 Inorganic nanoparticles

Inorganic nanoparticles are nanoscale materials composed of non-carbon-based elements or compounds. These particles, typically ranging from 1 to 100 nanometres in size (as shown in fig 5.2), exhibit unique physical and chemical properties due to their small dimensions and high surface area-to-volume ratio. Inorganic nanoparticles can be synthesized from various materials, including metals (e.g., gold, silver), metal oxides (e.g., iron oxide, titanium dioxide), and semiconductors (e.g., quantum dots) [30, 31]. The synthesis of inorganic nanoparticles can be achieved through various methods, such as chemical reduction, sol-gel processes, and hydrothermal techniques. These methods allow for precise control over particle size, shape, and composition, enabling the tailoring of nanoparticles for specific applications [32, 33]. Inorganic nanoparticles find applications across numerous fields, including medicine, electronics, energy, and environmental remediation. In medicine, they are used for drug delivery, imaging, and diagnostics [34]. For instance, iron oxide nanoparticles serve as contrast agents in magnetic resonance imaging, while gold nanoparticles are employed in photothermal therapy for cancer treatment. In electronics, semiconductor nanoparticles are utilized in the development of next-generation displays and solar cells [35]. Titanium dioxide nanoparticles are widely used in sunscreens and self-cleaning surfaces due to their photocatalytic properties. Additionally, inorganic nanoparticles play a crucial role in environmental applications, such as water purification and air filtration. The unique properties of inorganic nanoparticles, including their optical, magnetic, and catalytic characteristics, continue to drive research and innovation across various scientific disciplines [36, 37].

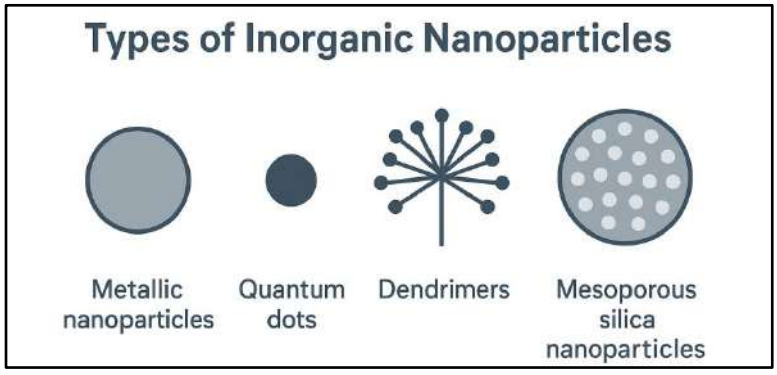

Figure 5.2: Different sources for inorganic nanoparticle formulations

3. Design Considerations for Sustained Brain Delivery

3.1 Size and Surface Properties

The size and surface properties of nanoparticles play a crucial role in determining their behaviour and applications. Nanoparticle size typically ranges from 1 to 100 nanometres, with this small scale resulting in a high surface area-to-volume ratio. This increased surface area enhances reactivity and catalytic activity, making nanoparticles ideal for various applications in catalysis, sensing, and drug delivery [38]. Surface properties, including charge, hydrophobicity, and functionalization, significantly influence nanoparticle interactions with their environment. Surface charge affects colloidal stability and particle-particle interactions, while hydrophobicity determines solubility and dispersion characteristics. Surface functionalization allows for the attachment of specific molecules or ligands, enabling targeted delivery or enhanced compatibility with different systems [39]. The size and surface properties of nanoparticles can be tailored during synthesis or through post-synthesis modifications. Controlling these parameters enables the fine-tuning of nanoparticle behaviour for specific applications [40]. For instance, smaller nanoparticles may exhibit enhanced permeability in biological systems, while larger ones may be more suitable for certain optical applications. Understanding and manipulating size and surface properties are essential for optimizing nanoparticle performance in various fields, including medicine, electronics, and environmental remediation. Ongoing research continues to explore novel methods for precise control over these properties, expanding the potential applications of nanoparticles across diverse disciplines [41, 42].

3.2 Drug Loading and Release Kinetics

Drug loading and release kinetics are critical aspects of nanoparticle-based drug delivery systems. The efficiency of drug loading depends on factors such as nanoparticle composition, drug properties, and loading methods. Common techniques include physical entrapment, adsorption, and chemical conjugation. The drug loading capacity is influenced by the nanoparticle's surface area, porosity, and interactions with the drug molecules [43, 44]. Release kinetics describe the rate and pattern of drug release from nanoparticles. Various mechanisms govern this process, including diffusion, erosion, and stimuli-responsive release. Diffusion-controlled release occurs as the drug moves from areas of high concentration within the nanoparticle to the surrounding environment [45]. Erosion-based release involves the degradation of the nanoparticle matrix, gradually exposing and releasing the encapsulated drug. Stimuli-responsive systems can be designed to release drugs in response to specific triggers such as pH changes, temperature, or enzymatic activity. The release profile can be tailored by modifying nanoparticle properties like size, composition, and surface characteristics [46]. Smaller nanoparticles generally exhibit faster release rates due to their larger surface area-to-volume ratio. Polymer-based nanoparticles can be engineered to have different degradation rates, affecting the release kinetics. Surface modifications can also influence drug-nanoparticle interactions and subsequent release patterns. Understanding and

optimizing drug loading and release kinetics are essential for developing effective nanoparticle-based drug delivery systems, ensuring appropriate drug concentrations at target sites while minimizing side effects [47, 48].

3.3 Targeting Strategies

Targeting strategies in drug delivery systems aim to enhance therapeutic efficacy while minimizing side effects. These strategies can be broadly categorized into passive and active targeting approaches. Passive targeting relies on the enhanced permeability and retention (EPR) effect, where nanoparticles accumulate preferentially in tumour tissues due to their leaky vasculature and poor lymphatic drainage [49]. This approach is particularly effective for solid tumours but has limitations in treating metastatic or diffuse diseases. Active targeting involves the modification of nanoparticle surfaces with ligands that specifically bind to receptors overexpressed on target cells. Common ligands include antibodies, peptides, aptamers, and small molecules [50]. This strategy enhances cellular uptake and intracellular drug accumulation in target tissues. Stimuli-responsive targeting utilizes the unique characteristics of diseased tissues, such as altered pH, temperature, or enzyme levels. Nanoparticles can be designed to release their payload only in response to these specific stimuli, further improving targeting precision. Magnetic targeting employs magnetic nanoparticles guided by external magnetic fields to concentrate drugs at desired locations. This approach is particularly useful for treating accessible tumours or vascular diseases. Cell-mediated targeting involves using cells, such as macrophages or stem cells, as carriers for nanoparticles. These cells naturally home to specific tissues or disease sites, providing a biological targeting mechanism. Combining multiple targeting strategies can synergistically enhance drug delivery efficiency and overcome biological barriers, leading to improved therapeutic outcomes [51, 52].

4. Overcoming the Blood-Brain Barrier

The blood-brain barrier (BBB) presents a significant challenge in treating neurological disorders due to its highly selective permeability. This protective barrier, composed of tightly packed endothelial cells, restricts the passage of most molecules, including therapeutic agents, into the brain. Overcoming the BBB is crucial for developing effective treatments for various neurological conditions. Several strategies have been developed to enhance drug delivery across the BBB [53]. One approach involves modifying drugs to increase their lipophilicity, allowing them to passively diffuse through the barrier. This method, however, often requires high doses and may lead to systemic side effects. Another promising technique is the use of nanoparticles as drug carriers. These particles can be engineered to cross the BBB through various mechanisms, such as receptor-mediated transcytosis. By coating nanoparticles with ligands that bind to specific receptors on the BBB endothelial cells, researchers can facilitate their transport across the barrier [54]. Temporary disruption of the BBB is another strategy being explored. Focused ultrasound, combined with microbubbles, can transiently open the BBB in specific regions, allowing for localized drug delivery. This

method offers the advantage of targeted delivery while minimizing systemic exposure. Cell-penetrating peptides have shown promise in facilitating the transport of drugs across the BBB [55]. These peptides can be conjugated to therapeutic agents, enhancing their ability to penetrate the barrier and reach the brain tissue. Intranasal drug delivery is gaining attention as a non-invasive method to bypass the BBB. This route exploits the olfactory and trigeminal nerve pathways, providing a direct connection between the nasal cavity and the brain [56]. Biological approaches, such as the use of exosomes or engineered cells, are also being investigated. These natural carriers can be loaded with therapeutic agents and possess inherent abilities to cross the BBB. Despite these advancements, overcoming the BBB remains a complex challenge. Combining multiple strategies and developing novel approaches will be crucial in improving drug delivery to the brain and advancing treatments for neurological disorders [57, 58].

5. Reported preclinical studies for brain related disorders

Table 5.1. List of polymer, formulation and dose description

Polymer used	Formulation formed	Herbal drug or phytoconstituents	Neurodegenerative disease	Animal species	Dose	References
Biodegradable polymeric nanocarrier (e.g., PLGA-based)	Curcumin-loaded polymeric nanoparticles	Curcumin (natural polyphenol)	Alzheimer's disease	Transgenic AD mice	systemic administration; improved neurogenesis & cognition reported	60
PLGA (and liposomes for comparison)	Rivastigmine-loaded PLGA nanoparticles & liposomes; intranasal delivery	Rivastigmine (synthetic cholinesterase inhibitor)	Alzheimer's disease	Wistar rats	reported higher brain bioavailability vs oral; improved behavioural memory performance	
PLGA	Rivastigmine tartrate–loaded PLGA nanoparticles	Rivastigmine tartrate	Alzheimer's disease	Rodents (rats, in vivo brain delivery)	enhanced brain delivery, sustained release properties	61
PEG-PLGA (Lf surface ligand)	Lactoferrin-modified PEG-PLGA nanoparticles (Lf-PEG-PLGA NPs) loaded with	synthetic drug: rotigotine	Parkinson's disease	Mice (Kunming)	rotigotine used DiR at 0.25 mg/kg intranasal to track NP	62

	rotigotine; intranasal, nose-to-brain; striatal targeting				brain delivery)	
PLGA (surface co-modified with lactoferrin and borneol)	Lf/borneol co-modified polymeric NPs loaded with dopamine; intranasal nose-to-brain	endogenous neurotransmitter: dopamine	Parkinson's disease (6-OHDA rat model)	Rats (Sprague–Dawley)	dosing described as intranasal across NP variants during PK/PD experiments	63
PLGA (chitosan-coated)	Chitosan-coated PLGA NPs (CS-PLGA NPs) loaded with rasagiline; intranasal (compared with IV)	synthetic drug: rasagiline	Parkinson's disease	Rats (Wistar)	study reports higher brain AUC and Cmax for intranasal CS-PLGA NPs vs IV solution	64,65
PAMAM (G4) hydroxyl-terminated dendrimer	Dendrimer–CSF1R inhibitor conjugate (D-45113), systemic (i.p.)	small-molecule CSF1R inhibitor, non-herbal	Alzheimer's disease	5xFAD mice (C57BL/6 background), mixed sex	200 mg/kg i.p., twice weekly for 4 weeks (treatment); a separate tracer experiment used 55 mg/kg dendrimer-Cy5 for biodistribution.	66
PAMAM (generation 4, hydroxyl-terminated) dendrimer	Dendrimer–2-PMPA conjugate (D-2PMPA), systemic (i.p.)	synthetic small-molecule inhibitor of glutamate carboxypeptidase II, not herbal	Multiple sclerosis	C57BL/6 mice with experimental autoimmune encephalomyelitis (EAE)	20 mg/kg i.p., every 3 days for 3 weeks (beginning at disease onset); unconjugated 2-PMPA control given at equivalent molar doses	67

					showed no efficacy.	
PLGA	Edaravone-loaded PLGA nanoparticles; chitosan nanoparticles (mucoadhesive) for nose-to-brain delivery	synthetic drug: edaravone	Amyotrophic lateral sclerosis (ALS)	Rodents (rats; intranasal preclinical studies)	reported improved brain delivery vs free edaravone; dosing concentration not specified in accessible sources	68
PLGA (PEGylated & peptide-labeled, e.g., pVEC)	Riluzole-loaded PLGA nanoparticles, surface-modified with PEG and BBB-targeting peptides	synthetic drug: riluzole	Amyotrophic lateral sclerosis (ALS)	Rodents (rats; in vivo component) + in vitro BBB cell models	improved BBB transport and brain targeting; in vivo delivery validated, but exact mg/kg dose not detailed in available summaries	69, 70
PLGA (polysorbate-80 coated for BBB penetration)	Peptide-loaded PLGA nanoparticles (QBP1, NT17-derived, PGQ9P2 anti-aggregation peptides)	synthetic/engineered therapeutic peptides, not herbal)	Huntington's disease	Drosophila HD model (motor performance); Healthy mice (BBB transport); in vitro cell models	studies describe dose-dependent aggregation inhibition and improved locomotion in flies; exact mg/kg peptide dosing in mice not provided in accessible abstracts	71
Polymeric/hybrid NP (brain-targeted, sustained release system)	Cholesterol-loaded nanoparticles for long-term release in brain	endogenous lipid: cholesterol	Huntington's disease	HD mouse model	reported rescue of synaptic function & cognitive deficits; administered repeatedly, but specific mg/kg dosing	72, 73

6. Challenges and Future Perspectives

Table 5.2: List of current challenges and future perspectives

Challenges	Blood-brain barrier (BBB) penetration	• Difficulty crossing the highly selective BBB • Need for specific surface modifications to enhance permeability
	Stability and circulation time	• Rapid clearance from bloodstream • Potential for aggregation or premature drug release
	Targeting specificity	• Ensuring nanoparticles reach intended brain regions • Minimizing off-target effects in other organs
	Toxicity and biocompatibility	• Potential neurotoxicity of nanoparticles • Long-term effects on brain function and structure
	Drug loading and release kinetics	• Optimizing drug encapsulation efficiency • Controlling sustained release over extended periods
Future perspectives	Advanced surface functionalization	• Developing novel ligands for improved BBB penetration • Dual-targeting strategies for enhanced specificity
	Stimuli-responsive nanoparticles	• pH-sensitive or enzyme-responsive systems • Magnetic or light-activated release mechanisms
	Combination therapies	• Co-delivery of multiple drugs or therapeutic agents • Synergistic effects for improved treatment outcomes
	Personalized medicine approaches	• Tailoring nanoparticle properties to individual patient needs • Integration with genomic and proteomic data
	In vivo imaging and tracking	• Real-time monitoring of nanoparticle distribution • Non-invasive assessment of therapeutic efficacy
	Scalable manufacturing processes	• Improving reproducibility and batch-to-batch consistency • Developing cost-effective production methods
	Regulatory considerations	• Establishing standardized protocols for safety assessment • Addressing long-term safety concerns for clinical translation

Conclusion

Polymeric nanoparticles and dendrimers offer promising platforms for sustained brain delivery, but face several challenges. The blood-brain barrier (BBB) presents a significant obstacle, requiring specific surface modifications to enhance permeability. Stability and circulation time are concerns, as rapid clearance and potential aggregation can limit effectiveness. Targeting specificity remains crucial to ensure nanoparticles reach intended brain regions while minimizing off-target effects. Toxicity and biocompatibility issues, including potential neurotoxicity and long-term effects on brain function, must be carefully addressed. Optimizing drug loading and release kinetics is essential for sustained delivery. Future perspectives for overcoming these challenges include advanced surface functionalization with novel ligands and dual-targeting strategies, development of stimuli-responsive nanoparticles, and combination therapies for synergistic effects. Personalized medicine approaches tailoring nanoparticle properties to individual patient needs show promise. Improved in vivo imaging and tracking techniques will enable real-time monitoring of nanoparticle distribution and therapeutic efficacy. Scalable manufacturing processes and regulatory considerations are critical for clinical translation. As research progresses, these versatile platforms have the potential to revolutionize sustained brain delivery, offering new treatment options for neurological disorders and improving patient outcomes.

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Conflicts of Interest

The authors declare that there are no conflicts of interest related to this work.

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