EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 8
Year: 2026

NANOPARTICLES FOR DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER: A COMPREHENSIVE REVIEW OF MECHANISMS, PLATFORMS, AND TRANSLATIONAL FRONTIERS

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DOI: https://doi.org/10.5281/zenodo.21884179

How to cite this Article: [1]Rohit Singh, [2]*Dr. Nidhi Chauhan, [3]Dr. Vaishali Patel, [4]Rozina P. Pravin. (2026). Nanoparticles for Drug Delivery Across the Blood-Brain Barrier: A Comprehensive Review of Mechanisms, Platforms, and Translational Frontiers. European Journal of Biomedical and Pharmaceutical Sciences, 13(8), 310–314.

Article Received on 14/07/2026 **Article Revised on 04/08/2026** **Article Published on 10/08/2026**

ABSTRACT

Central nervous system (CNS) disorders—including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and glioblastoma multiforme (GBM)—impose a mounting global healthcare burden, yet remain poorly treatable due to the blood-brain barrier (BBB), which restricts >98% of small-molecule drugs and virtually all large-molecule biologics from reaching the brain. Engineered nanoparticles (NPs), ranging from 1–1000 nm, have emerged as a transformative solution by exploiting unique physicochemical properties—tunable surface chemistry, high surface-area-to-volume ratios, and dual payload capacity—to circumvent BBB restrictions. This review comprehensively examines nanoparticle-mediated BBB drug delivery, covering the structural biology of the neurovascular unit (NVU), disease-specific BBB heterogeneity, and four major NP platforms: lipid-based (LNPs), polymeric (PNPs), metallic/inorganic (MNPs), and biomimetic cell membrane-coated nanoparticles (BMCNPs). Key transport mechanisms—receptor-mediated transcytosis (RMT), adsorptive-mediated transcytosis (AMT), carrier-mediated transport, and Trojan horse cell-based delivery—are critically evaluated. Advanced strategies including PEGylation, focused ultrasound (FUS), and intranasal delivery are discussed alongside translational evidence across AD, PD, and GBM. Finally, we address the critical barriers to clinical translation—the affinity paradox, post-BBB transport constraints, immunogenicity, scalability, and regulatory hurdles—and propose a precision, disease-informed nanomedicine framework as the path to clinical success.

KEYWORDS: *blood-brain barrier; nanoparticles; drug delivery; receptor-mediated transcytosis; lipid nanoparticles; polymeric nanoparticles; biomimetic nanoparticles; neurodegeneration; glioblastoma; focused ultrasound; PEGylation; neuro-nanomedicine.*

INTRODUCTION

The blood-brain barrier (BBB), while an evolutionary masterpiece protecting CNS homeostasis, paradoxically restricts >98% of small-molecule drugs and effectively 100% of large-molecule therapeutics—monoclonal antibodies, gene therapies, and recombinant proteins—from reaching the brain.[1] This pharmacokinetic bottleneck renders conventional systemic treatments for devastating CNS diseases—including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and glioblastoma multiforme (GBM)—largely ineffective at safe doses, while dose escalation predictably causes severe peripheral toxicity.[1,3]

Engineered nanoparticles (NPs), typically 1–1000 nm in diameter, have emerged as a paradigm-shifting solution. By exploiting high surface area-to-volume ratios, tunable surface chemistries, and dual encapsulation capacity for hydrophilic and lipophilic payloads, nanocarriers can be engineered to navigate systemic circulation, evade immune clearance, and traverse the neurovascular unit.[3] This review provides a critical synthesis of contemporary NP platforms, BBB transport mechanisms, advanced delivery strategies, therapeutic applications, and the persistent translational hurdles that must be overcome to realize the clinical promise of precision neuro-nanomedicine.

Cytoarchitecture of the Neurovascular Unit (NVU)

The BBB is no longer conceived as a static wall but as the neurovascular unit (NVU)—a dynamic, interdependent multicellular microenvironment.[3] Its primary barrier is a continuous, non-fenestrated monolayer of brain microvascular endothelial cells (BMECs) sealed by dense tight junction (TJ) complexes. These TJs—composed of claudin-5, occludin, and junctional adhesion molecules (JAMs), anchored to the actin cytoskeleton via zonula occludens proteins (ZO-1, ZO-2, ZO-3)—render the paracellular route completely impassable for nanocarriers and large biologics.[3]

Beyond TJs, the NVU comprises: (i) pericytes—contractile mural cells regulating capillary tone and TJ induction; (ii) astrocytic end-feet—secreting TGF-β and GDNF to maintain BMEC restrictive phenotype and regulate neurovascular coupling; and (iii) microglia—resident CNS macrophages that, upon activation, release cytokines and matrix metalloproteinases (MMPs) that profoundly alter BBB permeability.[3] A dense array of ATP-binding cassette (ABC) efflux transporters on the apical BMEC surface—notably P-glycoprotein (P-gp/ABCB1), BCRP (ABCG2), and MRPs—actively expel pharmaceutical substrates back into systemic circulation, while CYP450 enzymes enzymatically degrade compounds in transit, constituting an additional biochemical barrier.[3,4]

Disease-Specific BBB Heterogeneity

A critical insight driving modern nanomedicine design is that the BBB is not uniform across disease states. In acute neuropathologies (stroke, TBI, GBM core), MMP-driven degradation of basement membrane and TJ proteins creates a 'leaky' barrier, enabling the Enhanced Permeability and Retention (EPR) effect for passive NP accumulation.[3] However, the infiltrative margins of GBM retain an intact BBB, and nanotherapies relying solely on EPR fail to eradicate these peripheral tumor cells, inevitably causing recurrence.[3]

In chronic neurodegeneration (AD, PD), macroscopic barrier integrity is largely preserved, yet profound functional impairment occurs. In AD, cerebral amyloid angiopathy (CAA) shifts receptor expression—upregulating RAGE (Aβ influx) and downregulating LRP-1 (Aβ efflux)—and intensifies efflux pump activity.[1] These disease-dependent differences demand fundamentally distinct nanocarrier physicochemical engineering, ligand selection, and pharmacokinetic modeling, making disease heterogeneity the cornerstone of precision nanomedicine.[3]

Mechanisms of Nanoparticle Transport Across the BBB

1 Receptor-Mediated Transcytosis (RMT)

RMT is the most clinically promising active transport mechanism.[1] Targeting ligands on the NP surface bind to receptors highly expressed on the luminal BBB endothelium, triggering clathrin- or caveolae-mediated endocytosis, active vesicular cytoplasmic trafficking, and basolateral exocytosis into the brain parenchyma.[3] Key targets include the transferrin receptor (TfR; targeted via transferrin, OX26 antibody), LRP-1 (targeted via Angiopep-2 peptide), insulin receptor (IR), and lactoferrin receptor (LfR).[1] A critical engineering insight—the 'affinity paradox'—reveals that excessively high ligand-receptor binding affinity prevents basolateral NP dissociation, trapping the carrier in lysosomes. Optimal RMT therefore requires calibrated moderate affinity: sufficient for apical endocytosis, yet weak enough for basolateral exocytosis and drug release.[4]

2 Adsorptive-Mediated Transcytosis (AMT) and Other Pathways

AMT exploits the net-negative glycocalyx on the luminal endothelial surface: cationic NPs (e.g., chitosan-based) electrostatically adsorb and are internalized. AMT offers higher transport capacity than RMT but lower tissue specificity, risking off-target peripheral accumulation.[3] Carrier-Mediated Transcytosis (CMT) hijacks GLUT1 or LAT1 nutrient transporters, primarily suited to small prodrugs like L-DOPA rather than bulky NPs.[1] The Trojan Horse strategy exploits immune cell diapedesis—loading NPs into monocytes or macrophages ex vivo that are subsequently recruited to sites of neuroinflammation or tumor, smuggling their payload across TJs via the cell's own transmigration machinery.[15]

Nanoparticle Platforms for CNS Drug Delivery

Table 1: Comparative Overview of Major Nanoparticle Platforms for BBB Drug Delivery.

Platform	Key Materials	Core Advantages	Representative CNS Application	Ref.
Lipid-Based NPs (LNPs)	Phospholipids, cholesterol, triglycerides, oils	High biocompatibility; dual hydrophilic/lipophilic loading; mimics cell membrane	BTL-SynO4 reduces α-synuclein in PD; nanoemulsions improve neuroprotective antioxidant delivery	[1,5]
Polymeric NPs (PNPs)	PLGA, PEG, chitosan, poly(ε-caprolactone)	Tunable degradation; stimuli-responsive cleavable linkers; precise size/shape control	PLGA-PEG-RVG29 NPs with rapamycin reduced microgliosis 60% in AD model	[2,4,8]
Metallic/Inorganic NPs (MNPs)	AuNPs, AgNPs, SPIONs, mesoporous silica	Unique optical/magnetic properties; theranostics; MRI contrast; magnetic hyperthermia	SPIONs induce 42–48°C intratumoral hyperthermia for GBM ablation; AuNPs detect Aβ/tau in AD	[7,21]
Biomimetic/Cell Membrane-Coated	RBC, platelet, macrophage,	Inherits complete surface proteome; immune evasion via	Triple-membrane hybrid (RBC+glioma+macrophage) for	[1,9,23]

NPs (BMCNPs)	tumor cell membranes	CD47; natural disease-site homing	targeted GBM; platelet-CCR2 hybrid reduced plaques in AD	

Lipid nanoparticles encompass liposomes, solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions. Their structural homology with biological membranes facilitates favorable thermodynamic interactions with the highly lipophilic BBB endothelium. SLNs overcome liposome instability via solid lipid matrices, while NLCs use a blended solid-liquid lattice to maximize drug loading and prevent payload expulsion during storage.[5]

Polymeric NPs offer unparalleled customizability. NP size directly dictates cellular uptake mechanisms; smaller particles penetrate the BBB more efficiently.[10] The key innovation of stimuli-responsive 'cleavable linkers' conjugates drugs to the polymer matrix via bonds that are stable in systemic circulation but cleave upon exposure to localized endosomal pH, redox potentials, or disease-specific enzymes—maximizing intracranial bioavailability while minimizing premature systemic drug leakage.[4]

Metallic NPs offer irreplaceable theranostic functionality. SPIONs serve simultaneously as MRI contrast agents and magnetic hyperthermia mediators for GBM thermal ablation.[7,21] However, ultra-small AuNPs (≤5 nm) can induce severe neuroinflammation and exacerbate BBB leakage, demonstrating that precise size calibration is essential.[4]

Biomimetic NPs represent the most paradigm-shifting advance. RBC membrane coatings inherit CD47 'self' proteins, inhibiting MPS clearance and dramatically prolonging circulation half-life.[17] Advanced multi-membrane hybrids integrate complementary functionalities—immune evasion, tumor targeting, and immunomodulation—in a single carrier that circumvents the immunogenicity limitations of synthetic ligand conjugation.[1,23]

Advanced Strategies for Enhanced BBB Penetration

PEGylation: Covalent coating with polyethylene glycol (PEG) creates a hydrophilic steric shield that masks NPs from opsonization and rapid RES clearance, massively prolonging systemic circulation half-life and increasing the probability of cerebral endothelium encounter.[1] Attaching targeting ligands (e.g., Angiopep-2, OX26) via flexible PEG tether chains reduces steric hindrance, preserving optimal 3D ligand conformation for receptor docking.[1]

Transcranial Focused Ultrasound (FUS): Low-intensity focused ultrasound combined with intravenous lipid microbubbles induces stable cavitation at targeted cerebrovascular coordinates, exerting localized mechanical force on endothelial cells that reversibly disassembles TJ proteins, upregulates caveolin-1-dependent transcytosis, and downregulates P-gp efflux activity.[1] This creates a temporary spatiotemporal delivery window without requiring surface targeting ligands. Application with calcium phosphate LNPs delivering SOD1 antisense oligonucleotides in ALS models dramatically decreased pathogenic SOD1 expression and improved motor neuron survival.[1] Tight junctions fully reassemble within hours after FUS cessation.

Intranasal Delivery: Depositing nanocarriers—nanoemulsions, NLCs, or SLNs—onto the olfactory and trigeminal nerve pathways in the upper nasal cavity enables direct CNS transport along neural tracts, entirely circumventing systemic circulation, hepatic first-pass metabolism, and BBB tight junctions.[1] Optimization must overcome rapid mucociliary clearance to maximize therapeutic absorption.[5]

Therapeutic Applications

Alzheimer's Disease: AuNP/AgNP surface plasmon resonance enables early non-invasive Aβ and tau biomarker detection in peripheral blood.[22] Therapeutically, hybrid platelet-CCR2 membrane liposomes have profoundly reduced amyloid plaque deposition, decreased neuroinflammation, and improved cognitive performance in familial AD transgenic models.[1] PLGA-PEG-RVG29 NPs delivering rapamycin reduced cortical microgliosis by 60% and restored novel-object recognition in transgenic mice.[2] The FDA approval of lecanemab (Leqembi) underscores the urgent need for nanocarriers capable of delivering large-molecule biologics across the BBB.[6]

Parkinson's Disease: Brain-Targeted Liposomes (BTLs) functionalized with RMT-targeting ligands have successfully delivered the monoclonal antibody SynO4 across the BBB and into dopaminergic neurons, actively inhibiting and reversing α-synuclein aggregation, leading to measurable improvements in motor function, gait, and spatial learning in preclinical PD models with a favorable safety profile.[1] SPIONs and AuNPs have been investigated for protected nerve growth factor (NGF) delivery to rescue degrading dopaminergic pathways.[7]

Glioblastoma Multiforme: GBM demands navigation of both the leaky BTB at the necrotic core (exploited via EPR) and the intact BBB at infiltrative margins (requiring active RMT targeting). Peptide-functionalized PNPs encapsulating chemotherapeutics drastically reduce systemic toxicity vs. conventional agents.[4] SPIONs under alternating magnetic fields deliver localized hyperthermia (42–48.5°C) for targeted thermal ablation without affecting adjacent healthy brain tissue.[21] Gadolinium-based NPs (AGuIX) act as radiosensitizers, amplifying whole-brain radiotherapy efficacy in metastatic disease.[4]

Barriers to Clinical Translation

Preclinical-Clinical Mismatch: NPs optimized in healthy young murine models routinely fail in human patients whose BBB receptor expression, permeability, and inflammatory status have been radically altered by specific pathologies, disease stage, and aging.[3] A NP dependent on TfR-RMT will fail categorically if the target disease downregulates TfR on the cerebral endothelium—a variable frequently missed in animal testing.[3]

Post-BBB Transport Constraints: Successful BBB crossing is necessary but insufficient. NPs must then navigate the dense, tortuous brain extracellular matrix, achieve specific secondary cellular uptake in diseased target cells, and execute proper intracellular trafficking for endosomal escape to prevent lysosomal payload degradation.[3] Failure at any post-BBB stage yields therapeutic failure despite successful barrier crossing.

Systemic Clearance and Immunogenicity: Without adequate stealth properties, NPs are rapidly opsonized and sequestered by the mononuclear phagocyte system (MPS), accumulating in the liver and spleen with potential hepatotoxicity.[3] Complex surface functionalization with foreign-derived antibodies or synthetic peptides increases immunogenicity, risking anaphylaxis or exacerbated neuroinflammation—particularly critical with repeated chronic dosing in neurodegenerative therapy.[2] Long-term heavy metal accumulation from MNPs remains a significant human trials barrier.[4]

Manufacturing and Regulatory Complexity: Translating multi-functional NPs from academic labs to GMP-compliant industrial production is immensely challenging. Ensuring strict lot-to-lot consistency for NPs simultaneously incorporating core polymers, cleavable linkers, targeting peptides, and biological payloads is exponentially difficult and financially prohibitive.[2,3] Regulatory agencies (FDA, EMA) face equivalent challenges evaluating these entities—which blur the boundaries between drug, device, and biologic—against the absence of standardized global protocols for their complex pharmacokinetic and toxicological characterization.[26]

Conclusions and Future Perspectives

The integration of advanced nanotechnology with targeted neuropharmacology represents a monumental paradigm shift in CNS disease treatment. Lipid, polymeric, metallic, and biomimetic nanoparticle platforms have collectively demonstrated the ability to circumvent the formidable structural and biochemical defenses of the BBB, achieving unprecedented targeted therapeutic successes in preclinical models of AD, PD, ALS, and GBM. Sophisticated strategies—RMT with affinity-calibrated ligands, stimuli-responsive cleavable linkers, FUS-mediated transient BBB opening, and biomimetic membrane camouflage—have transformed the field from reliance on inefficient passive diffusion to precision-guided delivery.

However, realizing full clinical potential demands an urgent paradigm shift: abandoning the pursuit of monolithic universal delivery vectors in favor of a precision, disease-informed engineering framework where NP design is specifically tailored to the unique heterogeneous pathological BBB state of each patient at a specific disease stage.[3] Future research must equally prioritize post-BBB interstitial dynamics, specific neural cell targeting, and intracellular trafficking alongside barrier penetration. Bridging the translational gap demands interdisciplinary collaboration among materials scientists, neurobiologists, pharmacologists, manufacturing engineers, and clinical regulators—standardizing GMP manufacturing processes, establishing global regulatory frameworks, and rigorously characterizing long-term immunological and toxicological NP impacts. Through this concerted, precision-driven approach, neuro-nanomedicine holds genuine promise of delivering safe, effective, and life-altering therapeutics to the millions of patients worldwide afflicted by devastating neurological diseases.[1]

ABBREVIATIONS

Aβ: Amyloid-beta; AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; AMT: Adsorptive-mediated transcytosis; AuNP: Gold nanoparticle; BBB: Blood-brain barrier; BMCNP: Biomimetic cell membrane-coated nanoparticle; BMEC: Brain microvascular endothelial cell; BTB: Blood-tumor barrier; CAA: Cerebral amyloid angiopathy; CMT: Carrier-mediated transcytosis; CNS: Central nervous system; EPR: Enhanced permeability and retention; FUS: Focused ultrasound; GBM: Glioblastoma multiforme; LNP: Lipid-based nanoparticle; LRP-1: Low-density lipoprotein receptor-related protein-1; MNP: Metallic nanoparticle; MPS: Mononuclear phagocyte system; NLC: Nanostructured lipid carrier; NP: Nanoparticle; NVU: Neurovascular unit; PD: Parkinson's disease; PEG: Polyethylene glycol; PLGA: Poly(lactic-co-glycolic acid); PNP: Polymeric nanoparticle; RBC: Red blood cell; RMT: Receptor-mediated transcytosis; SLN: Solid lipid nanoparticle; SPION: Superparamagnetic iron oxide nanoparticle; TBI: Traumatic brain injury; TfR: Transferrin receptor; TJ: Tight junction.

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