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Review

Synthetic Polymer Based Nano Drug Delivery Systems for Precise Alzheimer's Disease Therapy

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Abstract

Alzheimer's disease (AD) remains a major global health challenge due to its multifactorial pathology and the limited efficacy of existing therapies, which largely provide symptomatic relief without altering disease progression. A central obstacle to effective treatment is the blood–brain barrier (BBB), which severely restricts the delivery of therapeutics to the central nervous system. In this context, synthetic polymer–based nanoparticles have emerged as versatile platforms capable of improving drug stability, prolonging systemic circulation, and enabling controlled and targeted delivery across the BBB. This review summarizes recent advances in polymeric nanocarriers for AD therapy, with emphasis on translationally relevant systems, including poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(lactic acid)–poly(ethylene glycol) (PLA–PEG), and polyethyleneimine (PEI). We discuss how polymer chemistry, degradation kinetics, and surface functionalization can be rationally engineered to overcome key delivery barriers, while critically addressing inherent trade-offs such as long-term biodegradability and clearance (PCL) and the balance between cytotoxicity and transfection efficiency (PEI). Emerging polymeric architectures, including dendrimers and hybrid systems, are also highlighted for their potential to support multifunctional and tunable delivery strategies. Importantly, we emphasize the increasing role of advanced human-relevant *in vitro* models—such as brain organoids and BBB-on-a-chip platforms—supported by recent regulatory initiatives promoting New Approach Methodologies (NAMs). These systems provide more predictive tools for evaluating nanoparticle transport, safety, and therapeutic response, thereby strengthening translational confidence. Collectively, this review argues that successful clinical translation of polymer-based nanotherapies for AD will depend on the development of hybrid polymer systems validated in advanced human models, alongside early consideration of manufacturability and regulatory alignment.

Keywords

Alzheimer's disease, synthetic polymeric nanoparticles, controlled drug delivery, blood-brain barrier, brain organoids, organ-on-a-chip, regulatory science

1. Introduction

Alzheimer's disease (AD) is a gradual and irreversible neurodegenerative disease, characterized by cognitive, memory, and behavioral impairments that ultimately lead to total dependence on caregivers [1]. Globally, the incidence of AD and other dementias reached 7.24 million new cases in 2019—a 147.95% increase since 1990—making AD the most prevalent dementia type and a major global health issue [2]. Similarly, in the United Arab Emirates (UAE) and the broader Middle East and North Africa (MENA) region, AD is emerging as a significant concern. As of 2019, the age-standardized prevalence of dementia in the MENA region was 777.6 per 100,000 population, which represents a 3.0% increase compared to 1990 [3]. This rise has been attributed to an

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aging population, improved diagnostic rates, and the high prevalence of risk factors such as hypertension.

From a pathological standpoint, AD is marked by two main hallmarks: extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). Aβ plaques result from aberrant cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase, producing various Aβ isoforms, notably the aggregation-prone Aβ42 [4,5]. NFTs form when tau protein becomes hyperphosphorylated, destabilizing microtubules and impairing axonal transport [6]. This tau pathology spreads in a predictable pattern, known as Braak staging, starting in the entorhinal cortex and hippocampus before extending to neocortical areas.

There are two main types of Alzheimer's disease: sporadic Alzheimer's disease (SAD) and familial Alzheimer's disease (FAD). SAD (late-onset AD) is the most common type, influenced by genetic and environmental factors [7]. Although no single gene definitively causes SAD, the apolipoprotein E (APOE) ε4 allele significantly increases risk by elevating Aβ levels and promoting neuroinflammation [8]. The *APOE* gene, responsible for lipid metabolism and Aβ removal, contributes to higher levels of Aβ, neuroinflammation, and oxidative stress in carriers of the ε4 allele. Additional genes identified through genome-wide association studies, including triggering receptor expressed on myeloid cells 2 (*TREM2*), clusterin (*CLU*), phosphatidylinositol-binding clathrin assembly protein (*PICALM*), and bridging integrator 1 (*BIN1*), also influence Aβ metabolism, tau protein processing, lipid metabolism, and neuroinflammation [6]. Environmental contributors—such as hypertension, diabetes, obesity, and traumatic brain injury—can exacerbate vascular damage, impair Aβ clearance, and trigger chronic inflammation [7,9].

By contrast, FAD (early-onset AD) accounts for a smaller fraction of AD cases and typically follows an autosomal dominant pattern. Mutations in the APP gene near β- and γ-secretase sites raise the production of toxic Aβ42, while variants in presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) disrupt γ-secretase function, further increasing the Aβ42-to-Aβ40 ratio [10]. These mutations accelerate amyloidosis and tauopathy, leading to pronounced neurodegeneration.

Current AD treatments rely on cholinesterase inhibitors (ChEIs) and an N-methyl-D-aspartate (NMDA) receptor antagonist, both of which help manage symptoms but do not modify disease progression. ChEIs—such as donepezil, rivastigmine, and galantamine—preserve acetylcholine levels by inhibiting its breakdown, while memantine mitigates glutamate-induced excitotoxicity [11–14]. Despite their clinical utility, these drugs neither address the underlying pathophysiology nor prevent progressive neuronal damage, and their side effects can hinder long-term adherence [15].

A major obstacle to more effective therapies is the blood-brain barrier (BBB; Fig. 1), a physiological gateway that restricts drug delivery to the central nervous system, including potential treatments targeting Aβ plaques and tau tangles [16–18]. Adverse effects—for example, gastrointestinal discomfort associated with ChEIs or dizziness and confusion linked to memantine—further complicate treatment adherence [19]. Most importantly, no existing drug successfully alters the core AD pathologies, revealing a critical need for novel strategies.

Nanoparticle (NP) technology offers promising solutions by harnessing nanoscale materials to improve the targeting, uptake, and bioavailability of therapeutic compounds within the brain [15,20–24]. Lipid-based systems, such as liposomes and solid lipid nanoparticles, are biocompatible and simple to fabricate but offer limited long-term drug release, posing challenges in chronic AD treatment. Exosomes are low in immunogenicity and exhibit intrinsic targeting features, yet large-scale isolation and heterogeneity hinder their clinical viability [25,26]. Metallic nanoparticles (e.g., gold, iron oxide) excel in imaging and theranostics but can accumulate in tissues due to slow biodegradation, raising safety concerns over extended use [27,28].

In contrast, synthetic polymeric nanoparticles made from biodegradable materials like poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), or poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) offer notable advantages for AD therapy. Their composition can be tailored to control drug release profiles, enabling sustained delivery over weeks—critical in a progressively degenerative disease. Polymer degradation yields non-toxic byproducts (e.g., lactic and glycolic acids), reducing long-term toxicity. Surface modifications allow specific

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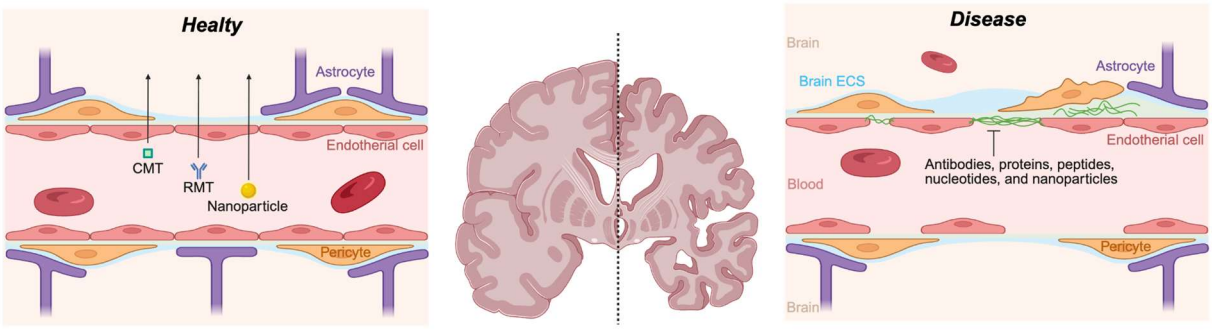

Figure 1: Biological barriers and transport pathways relevant to polymer-based nano drug delivery for Alzheimer's disease. Schematic illustration of the blood–brain barrier (BBB) and the major transport mechanisms governing therapeutic access to the central nervous system [16,17]. The BBB is formed by tightly connected brain endothelial cells supported by pericytes and astrocytic end-feet, creating a highly selective interface that limits the penetration of most systemically administered drugs. Polymeric nanoparticles can exploit endogenous transport pathways, including carrier-mediated transport (CMT) and receptor-mediated transcytosis (RMT), to facilitate BBB crossing. CMT relies on specific membrane transporters for small molecules, whereas RMT enables vesicular transport through ligand–receptor interactions (e.g., transferrin or lipoprotein receptors). After transcytosis, therapeutics are released into the brain extracellular space (ECS), where their diffusion and distribution determine access to neuronal and glial targets. The right panel highlights representative neurological disease contexts, including Alzheimer's disease, in which BBB dysfunction and altered ECS properties contribute to impaired drug delivery and therapeutic efficacy. Together, the figure illustrates how polymer-based nanocarriers are designed to overcome BBB-associated delivery constraints and improve central nervous system targeting. Created in BioRender. Kamei, K. (2026) https://BioRender.com/nw9ilmy

binding to Aβ or hyperphosphorylated tau, improving blood-brain barrier penetration and minimizing off-target effects. Lower immunogenicity than metallic or lipid-based formulations further enhances their safety, making polymeric nanoparticles promising vehicles for diverse therapeutic agents, including biologics and gene-editing tools, in AD treatment.

Given the limitations of current AD therapies and the challenges posed by the BBB, synthetic polymeric nanoparticles present a compelling avenue for targeted, sustained drug delivery. Their tunable release profiles, biocompatibility, and potential for surface functionalization enable enhanced penetration of neuronal tissues, making them particularly well-suited to addressing the multifaceted pathology of AD. This review will therefore focus on the design, properties, and therapeutic implications of synthetic polymeric nanoparticles, examining how they may overcome current treatment barriers and pave the way for more effective, disease-modifying strategies in AD.

2. Literature Survey Strategy

This review was conducted as a narrative literature survey rather than a systematic review. Relevant publications were identified through comprehensive searches of PubMed, Google Scholar, Scopus, and Google, supplemented by manual screening of reference lists from key articles to identify additional pertinent studies not captured in the initial searches.

Searches were performed using combinations of keywords including, but not limited to: Alzheimer's disease, polymeric nanoparticles, synthetic polymers, drug delivery, gene delivery, blood–brain barrier, PLGA, PCL, PLA–PEG, polyethyleneimine, dendrimers, brain organoids, and BBB-on-a-chip. Only English-language publications were considered.

In total, approximately 200 articles were downloaded and reviewed in full text. Literature selection was guided primarily by relevance to the topic, scientific rigor, and recency, with particular emphasis on studies published between 2018 and 2025. No formal quantitative inclusion or exclusion criteria were applied, consistent with the narrative nature of this review; however, articles that were peripheral to polymer-based nanocarriers, lacked sufficient methodological detail, or were redundant with more recent or comprehensive publications were excluded during the screening process. Consequently, only a subset of the initially screened articles was cited in the final manuscript.

Among the cited references, approximately 43% correspond to original experimental research articles, while 57% are review papers, reflecting an intentional balance between primary mechanistic studies and integrative perspectives. All cited works were available as full-text articles and were read in their entirety. A small

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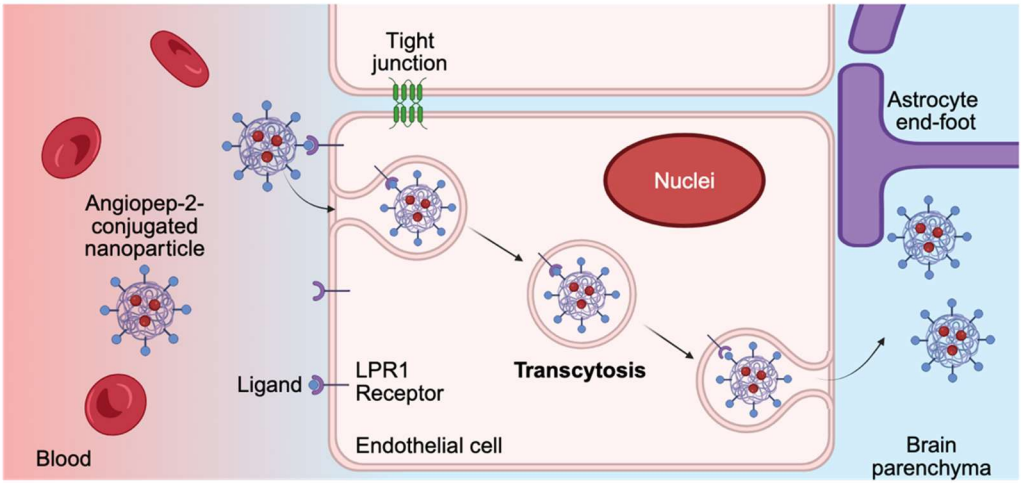

Figure 2: Receptor-mediated transcytosis (RMT) across the blood–brain barrier illustrated using Angiopep-2 as an example. Schematic representation of receptor-mediated transcytosis (RMT) across the blood–brain barrier (BBB). Angiopep-2 is a targeting peptide that selectively binds to low-density lipoprotein receptor–related protein 1 (LRP1), which is highly expressed on brain endothelial cells. Following ligand–receptor binding at the luminal surface, Angiopep-2–conjugated nanoparticles are internalized via endocytosis, trafficked across the endothelial cell, and released at the abluminal side into the brain parenchyma. This pathway enables the transport of therapeutic cargos that would otherwise be excluded by the BBB and represents a key strategy for enhancing central nervous system drug delivery. Astrocytic end-feet and endothelial cell interfaces contributing to BBB structure are also depicted. Created in BioRender. Kamei, K. (2026) https://BioRender.com/qk0q753

number of cited publications were authored or co-authored by the authors of this review; these were included solely where directly relevant to the topic and were evaluated using the same criteria applied to all other literature.

3. Brief History and Key Developments

Nanomedicine began taking shape in the mid-20th century with the exploration of nanoparticles (NPs) for medical applications. A foundational milestone was reached in the 1960s when Alec Bangham and colleagues first described liposomes, phospholipid vesicles that later became the basis for nanoparticle-based drug delivery systems [29]. In 1986, Matsumura et al. formally characterized the enhanced permeability and retention (EPR) effect, describing how the unique pathophysiological features of solid tumor vasculature enable the preferential accumulation of NPs [30]. By the late 1980s, the introduction of poly(ethylene glycol) (PEG) coatings on NPs significantly improved their ability to evade immune surveillance, thereby extending circulation time [31,32].

A major milestone in nanomedicine occurred in 1995 when the U.S. Food and Drug Administration (FDA) approved Doxil, a PEGylated liposomal formulation of doxorubicin, for the treatment of Kaposi's sarcoma [33]. This approval marked a significant breakthrough in NP-based drug delivery and demonstrated the clinical viability of nanoscale therapeutics. The success of Doxil underscored the potential of nanoparticle-based drug delivery, inspiring efforts to adapt similar strategies for neurodegenerative diseases.

As AD gained recognition as a major neurodegenerative disorder, researchers turned their attention to the challenge of delivering therapeutics across the blood-brain barrier (BBB). Advances in molecular biology identified specific targets such as Aβ plaques, highlighting the need for precise drug delivery into the brain [34]. By the early 2000s, research efforts intensified on designing nanoparticles capable of crossing the BBB, utilizing receptor-mediated transcytosis and exploiting regions where barrier integrity might be compromised in AD pathology.

During this period, researchers began functionalizing nanoparticles with ligands that selectively bind Aβ plaques, enabling targeted drug delivery [35,36]. Polymer-based nanoparticles—particularly those composed of biodegradable materials like poly(lactic-co-glycolic acid) (PLGA) [37] and poly(ε-caprolactone) (PCL) [38]—gained popularity due to their stability and ability to provide controlled, sustained drug release. These properties were particularly advantageous in AD models, where prolonged drug retention in the brain could potentially slow disease progression.

The versatility of polymeric nanoparticles further broadened their appeal; they can encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids [29]. Curcumin-loaded PLGA nanoparticles, for example, show promise in reducing amyloid aggregation and oxidative stress.[35] However, bioavailability challenges remain, and ongoing research explores nanomaterials—such as lipid nanoparticles and micelles—to enhance curcumin's solubility, stability, and BBB penetration while minimizing toxicity.

4. Blood-Brain Barrier (BBB) and Challenges in Drug Delivery

BBB is a highly selective, semipermeable border of endothelial cells that prevents solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system (CNS) where neurons reside (Figure 1) [16–18]. This barrier is formed by endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane [39]. The tight junctions between these endothelial cells are a key component, severely restricting the passage of substances from the bloodstream into the brain. While this barrier is crucial for protecting the brain from toxins and pathogens, it also poses a major challenge for the delivery of therapeutic agents to the CNS.

For a drug to cross the BBB, it generally needs to be small in molecular weight (typically under 400–600 Da) and be lipid-soluble to diffuse across the cell membranes [16,40]. However, nanoparticles can overcome this barrier through several mechanisms. Passive diffusion allows small, lipid-soluble drugs to cross naturally, while receptor-mediated transcytosis enhances transport via ligands targeting BBB receptors, such as transferrin or insulin receptors [41–45]. Adsorptive-mediated transcytosis exploits electrostatic interactions between positively charged nanoparticles and the negatively charged BBB surface, facilitating uptake and transport [46].

Among nanoparticle-based strategies, polymeric nanoparticles are particularly effective due to their biocompatibility, tunable properties, and ability to encapsulate drugs. Functionalization ensures targeted drug release, especially in reducing Aβ plaques and tau protein tangles [47]. One notable strategy is Angiopep-2-mediated transport, where Angiopep-2 binds to low-density lipoprotein receptor-related protein 1 (LRP1) on endothelial cells, triggering endocytosis and intracellular transport before releasing the therapeutic payload into brain tissue (Figure 2) [48]. Since LRP1 plays a role in Aβ clearance, Angiopep-2-modified nanoparticles enhance

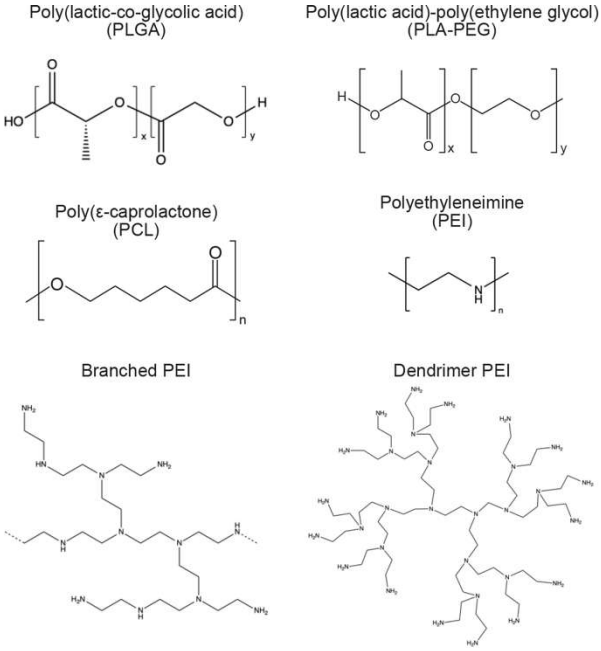

Figure 3: Structures of typical synthetic polymers forming nanoparticles for drug delivery in Alzheimer's Disease

drug delivery to affected regions, potentially reducing Aβ aggregation and tau pathology.

Nose-to-brain drug delivery offers a non-invasive alternative that bypasses the BBB entirely by leveraging the nasal cavity for direct drug transport to CNS [49,50]. This pathway minimizes systemic absorption while ensuring targeted delivery. Nanoparticles can reach the brain via the olfactory route, where they penetrate the olfactory epithelium and travel along the olfactory nerve to the olfactory bulb, or the trigeminal nerve pathway, where they are taken up by the respiratory epithelium and transported to deeper brain regions.

To enhance drug retention and absorption, NPs can be optimized for mucoadhesion—thereby reducing rapid clearance by mucociliary action—and for controlled release, which ensures sustained therapeutic effects [51]. Extracellular transport mechanisms, such as paracellular diffusion and transcytosis, further facilitate their passage between epithelial cells [52,53]. Together, these strategies make nanoparticle systems particularly effective for delivering anti-inflammatory agents aimed at mitigating AD-related neuroinflammation [53].

Despite its potential, nose-to-brain delivery faces challenges such as mucociliary clearance, which limits drug residence time, and the formation of protein coronas that may cause off-target interactions [54–56]. However, polymeric nanoparticles such as PLGA and chitosan, lipid nanoparticles, nanoemulsions, and

dendrimers show promise in protecting drugs from enzymatic degradation while improving absorption and bioavailability [20].

Both BBB delivery and nose-to-brain delivery offer promising strategies for nanoparticle-based AD therapies. While BBB-targeted approaches enable precise drug transport, nose-to-brain delivery provides a non-invasive route to the CNS. Continued advancements in nanoparticle engineering and transport optimization will be key to improving therapeutic efficacy in AD treatment.

5. Synthetic Polymeric Nanoparticles for Drug Delivery in Alzheimer's Disease

Several synthetic polymeric nanocarriers have been developed to improve drug delivery for AD. These systems leverage biocompatible, biodegradable polymers to encapsulate therapeutic agents, protect them from degradation, and release them in a controlled manner. Crucially, many polymeric NPs can be engineered to cross BBB via size control, surface modification (e.g. PEGylation or targeting ligands), and by tuning polymer properties like hydrophobicity and degradation rate [57]. In general, polymeric NPs offer sustained drug release, improved bioavailability in the brain, and reduced systemic toxicity compared to free drugs [58,59]. Below, we discuss key types of synthetic polymeric NPs in AD therapy – including PLGA, PCL, PLA-PEG copolymers, PEI-based polyplexes, and emerging polymeric systems – highlighting recent advances (2023–2025) in their design, therapeutic mechanisms, and clinical relevance (Figure 3).

5.1. Poly(lactic-co-glycolic acid) (PLGA)

PLGA is an FDA-approved, linear copolymer whose popularity in neuro-nanomedicine stems from its excellent biocompatibility, predictable hydrolytic degradation, and ease of formulation with both hydrophilic and hydrophobic payloads (Figure 3) [60–67]. By adjusting the lactic-to-glycolic ratio, researchers can fine-tune glass-transition temperature, crystallinity, and therefore drug-release kinetics; a 50:50 ratio, for instance, degrades within ~1 week, whereas PLA-rich variants may persist for >18 weeks *in vivo* [64,68]. Surface modification (e.g., PEGylation, ligand conjugation) further extends circulation time and enables receptor-mediated BBB transport [64]. Its low toxicity and ability to blend well with other polymers and additives [69] make it an ideal candidate for drug encapsulation [63,64,68].

Notably, recent studies indicate that PLGA itself may exert therapeutic effects beyond serving as a passive carrier [62,70]. Paul *et al.* demonstrated that drug-free ("native") PLGA nanoparticles (NPs) attenuate Aβ42 fibrillization and protect cortical neurons. This unexpected intrinsic activity suggests PLGA NPs might help ameliorate AD pathology by "soaking up" or interfering with toxic Aβ oligomers and tau aggregates [62]. Additionally, PLGA NPs are being explored for gene delivery in AD: for example, cationic-surface PLGA NPs loaded with siRNA against *Cdkn2a* ($p16^{INK4a}$) successfully silenced this aging-related gene in microglia, thereby "rejuvenating" microglial cells, enhancing their Aβ phagocytosis, and reducing amyloid plaque burden in AD mouse models [71]. This strategy led to improved cognitive outcomes, highlighting how PLGA nanocarriers can be tailored for immunomodulation in AD [72]. Overall, PLGA-based nanoparticles offer a versatile platform combining favorable safety (PLGA degrades into natural metabolites) with the flexibility to carry diverse therapeutic payloads and even confer some disease-modifying benefits on their own.

Tracy *et al*. showed that 200 nm PLGA-block-hyaluronic-acid nanoparticles preferentially accumulate in the hippocampi of 13- to 16-month-old APP/PS1 mice—and even age-matched wild-type mice—because BBB permeability increases with age. The HA corona binds the CD44 receptor on reactive astrocytes and activated microglia, giving dual benefits of (i) passive entry through "leaky" vasculature and (ii) active cellular uptake [73].

5.2. Poly(ε-caprolactone) (PCL)

Polycaprolactone (PCL) is another FDA-approved biodegradable polyester used in nanoparticle formulation [74], distinguished by its more hydrophobic nature and slower degradation kinetics relative to PLGA (Figure 3) [75]. These properties make PCL particularly attractive for applications requiring long-term, sustained drug release, although they also raise important questions regarding long-term polymer residence and biocompatibility in the central nervous system.

Early work by Mahmoudi *et al.* leveraged exploited PCL's slow erosion by encapsulating memantine (an NMDA-receptor antagonist) in PCL nanocapsules (MEM@PCL), achieving improved pharmacokinetics and reduced off-target toxicity [76]. Subsequently, the same group subsequently developed 7-methoxytacrine-loaded PCL nanocapsules, demonstrating controlled release of this rapidly metabolised cholinesterase inhibitor and superior in-vitro neuroprotection [77]. More recently, Müller *et al.* fabricated hot-melt-extruded PCL matrices containing 1–50 wt % galantamine hydrobromide, attaining near-zero-order release profiles suitable for ultra-long-acting oral therapy [78].

Beyond payload formulation, surface engineering has emerged as a powerful strategy to overcome PCL's intrinsic limitations in BBB transport. Gu et al. adopted a biomimetic approach, cloaking PCL nanoparticles with erythrocyte membranes and grafting the BBB-targeting peptide TGNYKALHPHN (TGN) [79]. These TGN-RBC-NPs markedly increased brain curcumin levels, attenuated neuroinflammation, preserved hippocampal neurons, and improved cognition in Alzheimer's disease mouse models, understanding the importance of surface functionalization in enhancing CNS delivery.

Despite these advances, the long-term fate of PCL nanoparticles in the brain persists longer than faster-degrading polymers, its long-term fate in the brain, particularly under chronic dosing, remains under investigation. Current *in-vivo* tracking studies are beginning to map PCL nanoparticle biodegradation and clearance, but definitive data on whether residual polymer or metabolites accumulate in neural tissue are still lacking. Establishing the chronic-use safety profile of PCL nanocarriers is therefore a critical next step before widespread clinical translation.

To address concerns related to the slow degradation and long-term tissue residence of poly(ε-caprolactone), several material engineering strategies have been explored. One common approach is copolymerization, such as blending PCL with faster-degrading polyesters including poly(lactic acid) (PLA) [80–82] or poly(lactic-co-glycolic acid) (PLGA) [83], which accelerates hydrolytic breakdown while preserving the mechanical stability and sustained-release characteristics of PCL [84]. The incorporation of hydrophilic blocks (e.g., PEG) or ester-rich segments increases water uptake and enhances enzymatic accessibility, thereby shortening *in vivo* residence time. Additional strategies include molecular-weight reduction [85], introduction of amorphous domains [86], and formulation of PCL-based nanocomposites with biodegradable additives [86], all of which modulate degradation kinetics without compromising drug-loading capacity. Collectively, these approaches aim to balance PCL's advantage of ultra-sustained drug release with improved long-term biocompatibility, an important consideration for chronic neurodegenerative indications such as Alzheimer's disease.

Collectively, these advances position PCL nanoparticles as a valuable complement to PLGA systems, offering ultra-sustained release and versatile surface modification options for central-nervous-system therapeutics, provided that forthcoming studies confirm their long-term clearance and safety.

5.3. Poly(lactic acid)-poly(ethylene glycol) (PLA-PEG)

PLA-PEG consists of a block copolymer composed of a hydrophilic polyethylene glycol (PEG) segment and a hydrophobic poly(lactic acid) (PLA) segment, providing the dual advantage of prolonged systemic circulation and efficient drug encapsulation (Figure 3) [87]. Typical PLA-PEG NPs fall in the 50–200 nm range—small enough to evade the reticulo-endothelial system yet large enough to avoid rapid renal filtration, and within the size window most favourable for transcytosis across the BBB [88]. The PEG "stealth" layer limits opsonisation and hepatic clearance, while the PLA block secures hydrophobic drugs inside a degradable matrix, giving PLA-PEG NPs a dual advantage of long systemic half-life and high encapsulation efficiency.

To traverse the BBB, researchers graft targeting ligands such as Angiopep-2 or transferrin onto the PEG shell, exploiting receptor-mediated transcytosis; brain uptake has been reported to rise three- to ten-fold with such modifications [42,61,89].

Therapeutically, ligand-decorated PLA-PEG carriers have excelled in Alzheimer's disease (AD) models. Donepezil-loaded PLGA-b-PEG NPs prolonged drug exposure, suppressed acetylcholinesterase more effectively than free donepezil, and improved Morris-water-maze performance in Aβ-infused rats [90]. Flash-nanoprecipitated ibuprofen/PLA-PEG NPs remained stable for 34 days and quadrupled cerebral ibuprofen levels, damping microglial activation *in vivo* [79]. Beyond pharmacology, combining NGF-loaded PEG-PLGA NPs with neural-stem-cell transplantation restored cholinergic neurons and rescued cognition in AD rats, underscoring the platform's compatibility with regenerative approaches [91].

5.4. Polyethyleneimine (PEI)

Polyethyleneimine (PEI) is a highly cationic polymer characterized by a density of primary, secondary, and tertiary amines, which confer strong proton-buffering capacity and exceptional nucleic acid–binding affinity (Figure 3) [92–95]. These properties underpin PEI's long-standing utility as one of the most efficient non-viral vectors for gene delivery, particularly for siRNA and plasmid DNA. Both linear and branched PEI chains can be assembled into dendrimeric or globular architectures, yielding nanoparticles with well-defined sizes (typically 20–200 nm), high surface-area-to-volume ratios, and multivalent amine presentation—features that are advantageous for intracellular delivery in neurodegenerative disease models, including AD [96].

Functionalization of PEI nanocarriers with targeting ligands (e.g., apolipoprotein E, transferrin, or BBB-shuttle peptides) promotes receptor-mediated transcytosis, enabling efficient brain uptake [53]. Following cellular internalization, PEI's strong cationic charge facilitates endosomal escape through the so-called "proton-sponge" effect, a critical requirement for efficient cytosolic delivery of nucleic acid therapeutics [97,98]. Consistent with this mechanism, Zhang *et al.* achieved approximately 88 % knock-down of *Bace1* after intraventricular injection of a PEI-based siRNA complex, leading to a ~60 % decrease in soluble Aβ and significant cognitive rescue in 5×FAD mice [99].

Despite these advantages, cytotoxicity remains the principal limitation of high-molecular-weight or highly branched PEI, arising from excessive membrane disruption and nonspecific electrostatic interactions with cellular components [100]. Consequently, substantial efforts have focused on mitigating PEI-associated toxicity while preserving its high transfection efficiency, leading to a well-recognized trade-off between biocompatibility and delivery performance [101].

PEGylation is one of the most widely adopted strategies to attenuate PEI cytotoxicity by partially shielding surface charges and reducing nonspecific protein adsorption [102]. Experimental studies have demonstrated that moderate PEG grafting significantly improves cell viability and serum stability, while excessive PEGylation can hinder cellular uptake and endosomal escape, resulting in reduced transfection efficiency [103]. These findings underscore the importance of carefully tuning PEG chain length and grafting density to balance safety and gene delivery efficacy.

Charge-attenuation approaches, including partial acetylation of PEI amines, represent an alternative strategy to reduce toxicity. Controlled acetylation decreases membrane damage and, in some cases, weakens polymer–nucleic acid interactions sufficiently to facilitate intracellular payload release, thereby maintaining or even enhancing transfection efficiency at intermediate modification levels [104]. In contrast, excessive neutralization can compromise nucleic acid condensation and cellular uptake, again highlighting the existence of an optimal modification window [105].

More recently, zwitterionic shielding strategies [106], such as grafting sulfobetaine or carboxybetaine moieties onto PEI, have emerged as effective means of suppressing protein fouling and cytotoxicity while retaining nucleic acid binding capability [107]. Original experimental studies show that mildly zwitterion-modified PEI complexes exhibit substantially reduced cytotoxicity and preserved gene-silencing activity, whereas extensive shielding can diminish uptake efficiency.

An orthogonal and complementary approach involves the use of low-molecular-weight (LMW) PEI, which inherently exhibits lower cytotoxicity but reduced transfection efficiency [108]. To overcome this limitation, LMW PEI units have been assembled into biodegradable or reversibly crosslinked networks that mimic the nucleic acid condensation capacity of high-molecular-weight PEI while degrading into less toxic fragments intracellularly. Such systems have demonstrated markedly improved safety profiles with only moderate reductions in transfection efficiency, substantially improving the overall therapeutic index [94,95].

Collectively, these modification strategies establish PEI as a highly tunable gene delivery platform, where cytotoxicity and transfection efficiency can be rationally balanced through molecular engineering. Rather than representing a fundamental limitation, the toxicity–efficacy trade-off of PEI has become a central design parameter, enabling the development of safer, application-specific PEI-based nanocarriers for nucleic acid delivery in neurodegenerative and broader biomedical contexts.

6. Comparative Analysis of Polymeric Nanocarriers

While the four polymers discussed—PLGA, PCL, PLA-PEG, and PEI—all serve the general purpose of drug delivery, a deeper analysis reveals critical distinctions in their mechanisms, ideal use cases, and translational potential. The choice of a polymer is not arbitrary; it is a strategic decision that profoundly influences the therapeutic outcome [109].

6.1. Drug Encapsulation and Release Kinetics: A Tale of Two Mechanisms

The ability to effectively load and release a therapeutic agent is arguably the most crucial function of a nanocarrier. Here, the physicochemical properties of the polymers dictate their performance (Table 1).

PLGA [110] and PCL [111], both being hydrophobic polyesters, excel at encapsulating hydrophobic drugs through methods like nanoprecipitation or emulsion evaporation. The drug is typically entrapped within the solid polymer matrix. The release is then governed by a combination of drug diffusion and polymer degradation. PLGA, with its amorphous structure and tunable lactic-to-glycolic acid ratio, generally exhibits a characteristic

Table 1. Comparative Analysis of Polymeric Nanocarriers for AD Therapy

Feature	PLGA	PCL	PLA / PLA-PEG	PEI
Primary Application	Versatile delivery of small molecules & biologics.	Long-term, sustained release of neuroprotective agents.	"Stealth" delivery of sensitive cargo (e.g., antibodies, siRNA).	Gene therapy (siRNA, plasmid DNA delivery).
Drug Compatibility	Primarily hydrophobic drugs within the core matrix.	Primarily hydrophobic drugs; high permeability.	Hydrophobic core + potential for hydrophilic drug conjugation to PEG shell.	Nucleic acids (negative charge) via electrostatic condensation.
Release Mechanism	Biphasic: Initial burst followed by sustained release via bulk erosion.	Zero-order, linear release over extended periods via surface erosion.	Core-shell diffusion and polymer erosion; tunable via PEG length.	Endosomal escape ("proton sponge" effect); triggered release of cargo.
BBB Transport Strategy	Limited passive diffusion; requires active targeting ligands (e.g., ApoE) for efficiency.	Very limited passive diffusion; requires active targeting ligands.	"Stealth" effect from PEG layer prolongs circulation, enhancing probability of crossing.	Adsorptive-mediated transcytosis due to positive surface charge.
Key Advantage	FDA-approved; highly tunable degradation & release profile.	Excellent for chronic, long-term therapy due to slow, steady release.	Prolonged blood circulation and enhanced BBB penetration.	Highest non-viral gene transfection efficiency.
Primary Challenge	Acidic degradation byproducts can harm labile drugs and cause inflammation.	Very slow degradation (residence time in brain); hydrophobicity limits drug types.	"PEG dilemma" (can hinder cellular uptake); potential for anti-PEG antibodies.	Inherent cytotoxicity due to high positive charge density.
Clinical Development Status	FDA-approved for multiple parenteral drug delivery applications; widely used in approved formulations and clinical trials [64,65,67].	FDA-approved polymer for biomedical applications; nanoparticle-based drug delivery systems primarily at preclinical and early translational stages [74,86].	FDA-approved (PLA) and clinically validated in multiple drug delivery systems; PLA–PEG block copolymers extensively used in clinical and preclinical nanomedicine [66,67,87].	Not FDA-approved for systemic drug delivery; extensively investigated in preclinical gene and nucleic acid delivery, with modified forms under translational evaluation [92–95].

biphasic release: an initial "burst release" of surface-adsorbed drug, followed by a slower, sustained release as the polymer matrix erodes [112,113]. This can be beneficial for therapies requiring an initial high dose followed by a maintenance dose. PCL, due to its semi-crystalline nature and slower degradation, offers a more linear, zero-order release profile over much longer periods (months to years) [114], making it ideal for

neuroprotective agents that require a constant, steady-state concentration in the brain.

PLA-PEG, as a diblock copolymer, forms core-shell nanoparticles. The hydrophobic PLA core is the primary site of drug encapsulation, similar to PLGA and PCL. However, the hydrophilic PEG shell can be used to conjugate or adsorb hydrophilic drugs or biologics, creating a dual-loading capacity [115]. The release profile is similar to PLGA but can be further modulated by the length of the PEG chain, which influences the nanoparticle's interaction with the surrounding aqueous environment.

PEI functions via a fundamentally different mechanism: it is engineered primarily for gene delivery rather than the controlled administration of small molecule drugs. Its highly cationic nature allows PEI to strongly bind, compact, and condense negatively charged nucleic acids (such as siRNA or plasmid DNA), forming polyplexes through electrostatic interactions [92,93,116]. Inside the cell, release of the genetic payload is not designed as a gradual diffusion process but as an "on-demand" event triggered by the so-called proton sponge effect in endosomes [97,98]. The buffering capacity of protonable amines in PEI causes accumulation of protons and counter-ions, osmotic swelling, and eventual endosomal rupture to liberate the nucleic acid cargo into the cytosol [117]. This mechanism is highly effective for gene delivery but is poorly suited to sustained release of conventional small molecule drugs, where a slow, predictable elution over time is desired.

6.2. Navigating the Blood-Brain Barrier: Stealth, Charge, and Targeting

Crossing the BBB is the primary rate-limiting step for most CNS drugs. Each polymer employs a different strategy to overcome this barrier.

PLA-PEG is the undisputed champion of "stealth" delivery. The dense layer of hydrophilic PEG on the nanoparticle surface effectively shields it from opsonization and clearance by the reticuloendothelial system. This dramatically increases its circulation half-life, providing a greater window of opportunity for the nanoparticle to interact with and cross the BBB [118]. While the exact mechanism is still debated, it is believed to involve a combination of passive diffusion and receptor-mediated transcytosis (RMT), possibly through interactions with receptors like LRP1 [119].

PLGA and PCL nanoparticles, in their unmodified state, have a more limited ability to cross the BBB [29]. Their passage is largely dependent on their small size and hydrophobic surface, which allows for some level of passive diffusion. However, to achieve clinically relevant brain concentrations, they almost always require surface functionalization with targeting ligands (e.g., antibodies against the transferrin receptor, peptides like ApoE) to engage in active RMT. This makes them highly versatile but also adds a layer of complexity to their design and manufacturing [120].

PEI utilizes its positive charge to its advantage. The NP's cationic surface can interact with the negatively charged components of the BBB endothelial cell membranes, triggering adsorptive-mediated transcytosis [121]. While effective, this mechanism is less specific than RMT and can lead to off-target effects and potential toxicity [116,122].

6.3. Biocompatibility and Toxicity: The Degradation Dilemma

The long-term safety of the nanocarrier is a paramount concern, especially for a chronic disease like AD.

PLGA and PCL are generally considered highly biocompatible, as they degrade into natural metabolites (lactic acid, glycolic acid, and 6-hydroxycaproic acid) that are cleared from the body. However, the devil is in the details. The degradation of PLGA creates an acidic microenvironment [123], which can be detrimental to the stability of encapsulated drugs and can potentially induce a localized inflammatory response [124]. PCL's very slow degradation rate, while beneficial for drug release, means that the polymer will reside in the brain for a very long time, and the long-term consequences of this are not yet fully understood.

PLA-PEG shares the biocompatibility of PLA, and the PEG component is also considered safe and is used in many FDA-approved drugs. However, there is some emerging concern about the potential for anti-PEG antibodies [125,126], which could lead to accelerated clearance of the nanoparticles upon repeated administration (the "accelerated blood clearance" or ABC phenomenon).

PEI is the most problematic of the four in terms of safety. Its high cationic charge density, which is essential for its function, is also the source of its inherent cytotoxicity. PEI can disrupt cell membranes and induce apoptosis. While this toxicity can be mitigated by using lower molecular weight PEI or by conjugating it with other polymers, it remains a major barrier to its clinical translation.

In conclusion, the choice of a synthetic polymer for AD therapy is a complex multi-parameter optimization problem. There is no single "best" polymer; rather, there is an "optimal" polymer for a specific therapeutic strategy. The future likely lies in the development of hybrid systems that combine the best

features of each of these materials to create truly "smart" and effective nanotherapies for Alzheimer's disease.

7. Emerging Polymeric Platforms

Beyond the cornerstone polymers, the field of nanomedicine is continually innovating, introducing novel platforms that offer unique advantages for CNS drug delivery. These emerging systems leverage distinct architectures and biological interactions to overcome the challenges of treating Alzheimer's disease.

7.1. Polyamidoamine (PAMAM) Dendrimers

Dendrimers represent a fascinating class of synthetic polymers with a highly branched, "tree-like" architecture. Unlike linear polymers, PAMAM dendrimers [127,128] are synthesized in a layer-by-layer fashion, resulting in a perfectly uniform and spherical nanostructure. This precise, monodisperse nature gives researchers unparalleled control over their physicochemical properties. The multivalent surface of PAMAM dendrimers can be densely functionalized with targeting moieties, imaging agents, and therapeutic drugs, creating a highly sophisticated, multi-functional nanodevice. Their unique structure and customizable surface have made them a powerful tool for crossing the BBB and have shown potential in both delivering anti-amyloid agents and acting as therapeutic agents themselves by inhibiting protein aggregation.

7.2. Polyanhydrides eroding layer-by-layer

Polyanhydrides are a class of biodegradable polymers distinguished by their surface-eroding degradation mechanism. Whereas polymers like PLGA degrade via bulk hydrolysis, which can lead to an unpredictable burst release, polyanhydrides erode cleanly from the surface inwards. This property results in a highly predictable, linear, zero-order drug release, which is ideal for therapies that require a constant, steady-state drug concentration. The FDA-approved use of a polyanhydride wafer implant (Gliadel®) for treating brain tumors has already established a clinical precedent for their safety and utility within the CNS, making them a strong candidate for future AD therapies [129,130].

8. Advanced *In Vitro* Models: Bridging the Gap in Preclinical Research

A significant hurdle in the development of AD nanotherapies is the reliance on traditional preclinical models that often fail to predict human responses. Standard 2D cell cultures lack the complex three-dimensional architecture and cell-type diversity of the brain, while animal models, despite their utility, have inherent species-specific differences that limit their translational relevance.

In response to these limitations, advanced human-relevant *in vitro* platforms have gained increasing attention, supported by recent initiatives promoting New Approach Methodologies (NAMs) from the U.S. Food and Drug Administration and the National Institutes of Health [131,132]. Brain organoids and organ-on-a-chip systems, including blood–brain barrier models, offer more physiologically relevant environments for evaluating nanoparticle transport, toxicity, and therapeutic efficacy, and are increasingly viewed as complementary tools for translational research and regulatory science.

Together, these platforms provide a promising framework for bridging the gap between preclinical development and clinical translation of polymer-based nanomedicines for AD.

8.1. Brain Organoids: Modeling AD Pathology in a Dish

Brain organoids are self-assembling, three-dimensional (3D) cultures derived from human pluripotent stem cells (hPSCs) [133–135]. These organoids can recapitulate key aspects of early human brain development, including the formation of distinct brain regions and the presence of diverse cell types like neurons, astrocytes, and microglia. For AD research, patient-derived hPSCs can be used to generate organoids that intrinsically develop AD-like pathology, such as amyloid-beta aggregation and hyperphosphorylated tau [136,137]. This provides an invaluable human-specific model, allowing researchers to apply polymeric nanoparticles and directly observe their efficacy in reducing Aβ plaques or tau tangles within a complex, multi-cellular environment. Furthermore, the intricate cell-cell interactions within these organoids enable a more accurate assessment of potential nanoparticle neurotoxicity than is possible with traditional 2D cultures [133,138].

8.2. Organs-on-a-Chip: Recreating the Blood-Brain Barrier

The concept of the *organ-on-a-chip* refers to a microfluidic device that houses living cells within

continuously perfused micro-channels, reproducing the physiological and mechanical environment of a human organ at microscale [139,140]. Of particular relevance to nanomedicine is the BBB-on-a-chip platform, which co-cultures human brain endothelial cells, pericytes, and astrocytes under dynamic flow conditions that replicate blood flow and shear stress. This configuration establishes a functional barrier that more closely resembles the *in vivo* human BBB than conventional static transwell systems, making it particularly valuable for translational studies [141–143].

These models play a crucial role in the development of nanomedicines. They provide a robust and reproducible means of testing and quantifying the ability of polymeric nanoparticles to cross the human BBB, with some platforms incorporating micro-electrode arrays to measure trans-endothelial electrical resistance (TEER) and thus track barrier integrity in real time [144]. Moreover, the live imaging and integrated sensing capabilities of BBB-on-a-chip systems allow researchers to directly observe the route of nanoparticle passage—such as receptor-mediated transcytosis versus paracellular leakage—thereby offering mechanistic insight critical for optimizing nanocarrier design [143].

The incorporation of BBB-on-a-chip platforms into the nanoparticle development pipeline has the potential to de-risk clinical translation by generating highly human-relevant preclinical data. When combined with brain organoid systems, these technologies enable a more predictive evaluation of nanoparticle safety, transport efficiency, and therapeutic efficacy, ultimately accelerating the advancement of promising nano therapies from the laboratory bench to the patients who need them most [139,140].

9. Economics and Regulatory Considerations

Global regulatory frameworks have progressively adapted to the specific challenges posed by polymer-based nanomedicines without fundamentally altering existing approval pathways. Major agencies, including the FDA, EMA, and PMDA, generally evaluate nanodrug delivery systems under established quality, safety, and efficacy standards, often using combination-product frameworks, while issuing supplementary guidance tailored to nanoscale materials [145]. Early engagement with regulators is widely encouraged, and reflection papers or product-class–specific guidelines have been introduced to address characterization, manufacturing, and risk assessment of nanomedicines [146–149]. Nevertheless, highly complex or multifunctional polymeric systems may still require case-by-case regulatory evaluation, underscoring the need for continued refinement of regulatory science.

In the Middle East and North Africa (MENA) region, regulatory capacity for nanomedicine remains heterogeneous but is rapidly evolving. Historically fragmented national approval processes have posed challenges for innovative therapies; however, increasing reliance on FDA and EMA approvals, along with emerging regional harmonization initiatives, is improving access pathways [147]. These developments suggest growing opportunities for advanced polymer-based nano drug delivery systems in MENA, provided that regulatory expertise and infrastructure continue to mature.

From an economic perspective, synthetic polymer–based nanomedicines face substantial translational barriers. Manufacturing under Good Manufacturing Practice (GMP) conditions is technically demanding and costly, particularly because nanoparticle fabrication often requires sterile processing, specialized equipment, and extensive quality control [145]. In addition, limited availability of contract manufacturing facilities with nanomedicine expertise frequently necessitates bespoke infrastructure or strategic partnerships. Product complexity further amplifies costs, as each added functional component (e.g., targeting ligands or imaging moieties) increases characterization and safety-testing requirements. These factors contribute to a persistent "valley of death," where many nanomedicine candidates fail to progress beyond preclinical development. Although more than 100 nanomedicines have been approved globally—predominantly in oncology [146]—no polymeric nanocarrier has yet reached clinical approval for AD [150], reflecting both the inherent challenges of CNS drug development and the added burden of demonstrating safe and effective brain targeting in clinical trials.

Despite these challenges, recent developments are encouraging. Advances in nano pharmaceutical manufacturing capacity, increased regulatory engagement through early scientific advice programs, and growing alignment between regulatory science and nanotechnology are collectively lowering barriers to translation [145]. Together, these trends are expected to facilitate more efficient evaluation and eventual clinical adoption of synthetic polymer–based nanoparticle therapies for Alzheimer's disease.

10. Outlook

Synthetic polymer–based nanoparticle platforms are expected to play an increasingly important role in Alzheimer's disease research and therapy, provided that

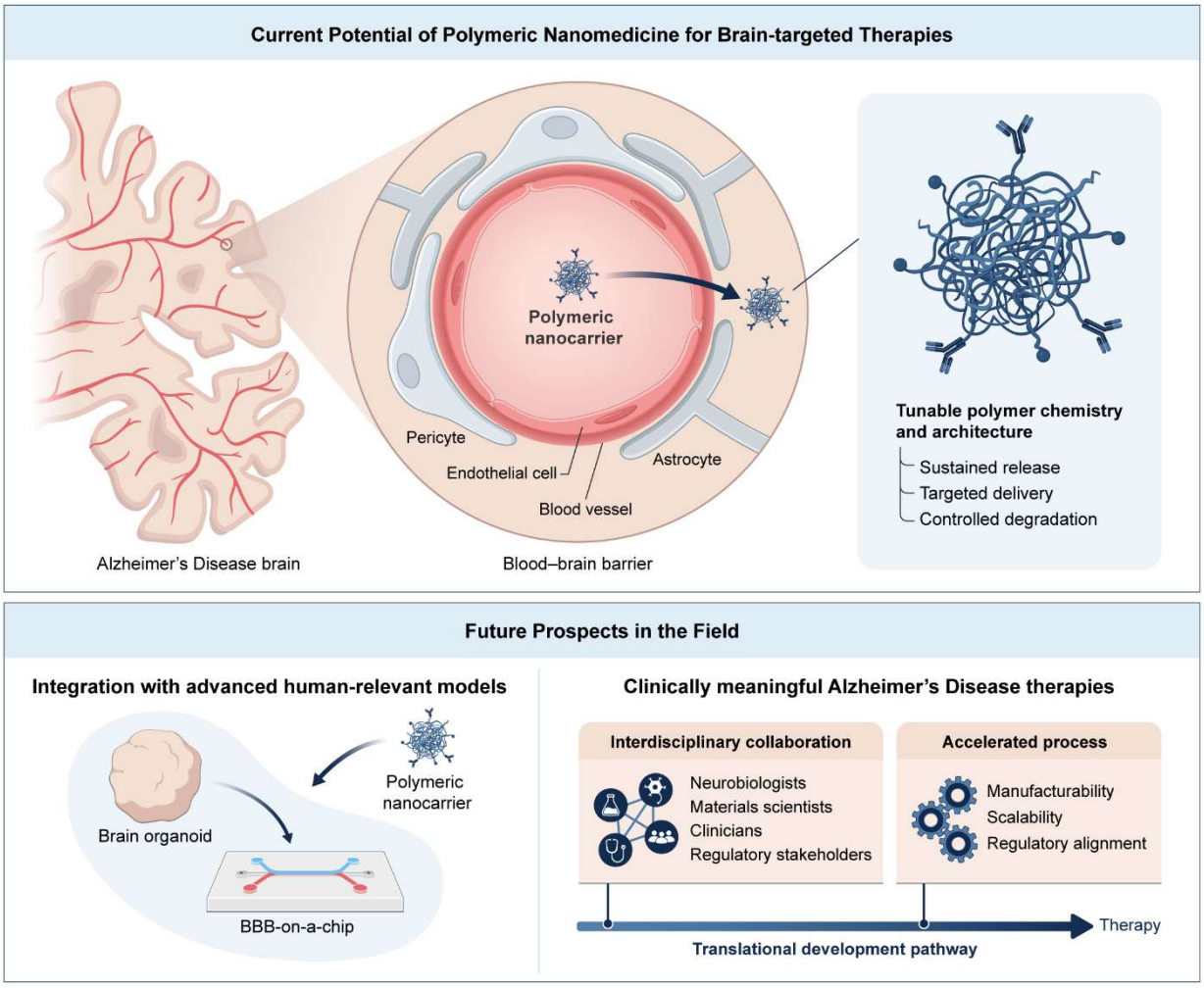

Figure 4: Future prospects of polymeric nanomedicine for brain-targeted Alzheimer's disease (AD) therapies. The upper panel summarizes the present capabilities of polymeric nanocarriers to overcome the blood–brain barrier (BBB) and deliver therapeutics to the AD brain. Polymeric nanocarriers interact with key components of the neurovascular unit, including endothelial cells, pericytes, and astrocytes, enabling brain entry through BBB transport mechanisms. Tunable polymer chemistry and architecture allow precise control over drug loading, sustained release, targeting specificity, and biodegradation profiles.
The lower panel illustrates future directions in the field, highlighting the integration of polymeric nanomedicine with advanced in vitro human-relevant models such as brain organoids and BBB-on-a-chip platforms to improve predictive power and mechanistic understanding. Clinically meaningful translation will require interdisciplinary collaboration among neurobiologists, materials scientists, clinicians, and regulatory stakeholders, alongside accelerated development pathways addressing manufacturability, scalability, and regulatory alignment, ultimately advancing polymer-based nanotherapeutics toward effective Alzheimer's disease treatments.

future development emphasizes biological relevance, translational feasibility, and regulatory alignment. Despite substantial progress in carrier engineering, safe and effective delivery across the blood–brain barrier and within the complex central nervous system microenvironment remains the principal challenge. Continued optimization of hybrid polymer architectures, surface functionalization strategies, and degradation-controlled systems will be essential to balance therapeutic efficacy with long-term biocompatibility.

An important direction for the field is the integration of polymeric nanocarriers with advanced human-relevant models, including brain organoids, BBB-on-a-chip platforms, and multi-organ microphysiological systems (Figure 4). These models offer more predictive assessment of nanoparticle transport, toxicity, and

therapeutic response than conventional animal models, and are expected to play a key role in both preclinical optimization and regulatory-relevant validation.

From a broader perspective, synthetic polymer-based nanoparticles have demonstrated versatility across diverse biomedical applications, including oncology and vaccine or antigen delivery. However, neurodegenerative diseases present distinct biological and translational constraints, particularly with respect to brain access and chronic safety, underscoring the importance of maintaining a disease-focused development strategy. In this context, future progress in Alzheimer's nanomedicine will depend on simplifying formulation complexity, ensuring scalable manufacturing, and incorporating regulatory considerations early in the design process.

Overall, the next phase of polymeric nanomedicine for Alzheimer's disease will be shaped by hybrid material systems validated in advanced human models, combined with pragmatic considerations of manufacturability and regulation. Strategic integration of materials science, neurobiology, and regulatory science will be critical for translating promising nano drug delivery concepts into clinically viable therapies.

11. Conclusion and Future Perspectives

Synthetic polymeric nanoparticles hold immense potential to revolutionize the AD treatment. By encapsulating therapeutic agents, these nanoparticles can protect them from degradation, prolong their circulation, and, most importantly, facilitate their transport across BBB. The tunability of polymer chemistry and architecture enables the rational design of drug delivery systems capable of sustained release, targeted delivery, and controlled degradation, directly addressing key limitations of current AD treatments.

Despite this potential, translation from preclinical development to clinical application remains challenging. Future efforts are expected to focus on the development of next-generation polymeric nanocarriers with improved targeting specificity, stimuli-responsive release profiles, and enhanced long-term safety. Increasing emphasis will also be placed on validation using advanced human-relevant models, such as brain organoids and BBB-on-a-chip platforms, to better capture human physiology and support regulatory decision-making.

Looking ahead, progress in polymeric nanomedicine for AD will depend on close collaboration among materials scientists, neurobiologists, clinicians, and regulatory stakeholders. Equally important will be early consideration of manufacturability, scalability, and regulatory alignment to ensure clinical feasibility. While polymer-based nanoparticles have demonstrated versatility across diverse biomedical applications, their successful translation in AD will require disease-focused design strategies that address the unique biological and safety constraints of the central nervous system. Although the path forward remains complex, continued interdisciplinary integration and technological refinement offer a realistic route toward clinically meaningful AD therapies.

Abbreviations

Aβ	Amyloid Beta
AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
BACE1	β-site Amyloid Precursor Protein Cleaving Enzyme 1
BBB	Blood–Brain Barrier
BBB-on-a-chip	Blood–Brain Barrier–on–a–chip
BIN1	Bridging Integrator 1
BoC	Body-on-a-Chip
CMT	Carrier-Mediated Transport
CNS	Central Nervous system
CLU	Clusterin
EPR	Enhanced Permeability and Retention
FAD	Familial Alzheimer's Disease
FDA	U.S. Food and Drug Administration
GMP	Good Manufacturing Practice
hPSC	Human Pluripotent Stem Cell
LMW	Low Molecular Weight
LRP1	Low-Density lipoprotein Receptor–related Protein 1
MEM@ PCL	Memantine-Loaded Poly(ε-caprolactone) Nano capsules
MENA / UAE	Middle East and North Africa / United Arab Emirates
NAMs	New Approach Methodologies
NFT	Neurofibrillary Tangle
NMDA	N-Methyl-D-Aspartate
NP	Nanoparticle
PAMAM	Polyamidoamine
PCL	Poly(ε-caprolactone)
PEI	Polyethyleneimine
PEG	Poly(ethylene glycol)
PET	Positron Emission Tomography
PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
PSEN	Presenilin
RMT	Receptor-Mediated Transcytosis
RNAi	RNA Interference
SAD	Sporadic Alzheimer's Disease
siRNA	Small Interfering RNA
TEER	Trans-Endothelial Electrical Resistance
TGN	TGNYKALHPHN Peptide

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Methodology: BA, NA, JA, FC, ZM, KK; Investigation: BA, NA, JA, FC, ZM, KK; Writing – Original Draft Preparation: BA, NA, JA, FC, ZM, KK; Writing – Review & Editing: BA, NA, JA, FC, ZM, KK; Visualization: BA, NA, JA, FC, ZM, KK; Supervision: KK; Project Administration: KK. All authors have reviewed and approved the published version of the manuscript.

Conflicts of Interest

KK is a founder and CTO of Z24 Holdings. The other authors declare no competing financial or personal interests that could have influenced the work reported in this paper.

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