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CHITOSAN-COATED POLYMERIC NANOPARTICLES FOR ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease remains a formidable therapeutic challenge, largely due to the blood- brain barrier restricting drug access to the central nervous system. We systematically synthesize preclinical evidence on chitosan-coated polymeric nanoparticles as a non- invasive intranasal delivery platform for targeted Alzheimer's therapy. Our central hypothesis is that the mucoadhesive and permeation-enhancing properties of chitosan coatings can significantly improve brain bioavailability and neurotherapeutic efficacy of both synthetic drugs and natural compounds. We conducted a systematic literature search in PubMed, Scopus, and Web of Science for studies published from 2010 onward, extracting data on nanoparticle physicochemical properties, cellular uptake, neuroimmune modulation, and pharmacokinetics. The retrieved studies exhibited substantial heterogeneity in core materials but consistently demonstrated that chitosan-coated systems enhanced brain- targeted delivery. For instance, a mannose-functionalized chitosan-coated PLGA system co-delivering cannabidiol and BDNF plasmid achieved a zeta potential of +31.7 mV and particle size of 306 nm, while a chitosan-coated liposomal donepezil system showed the highest cellular uptake efficiency of 66.8%. Neuroimmune modulation was evidenced by curcumin-encapsulated chitosan-coated PLGA nanoparticles reducing tumor necrosis factor-alpha levels to 70% of the positive control in BV-2 microglial cells. Furthermore, in vivo studies with synaptic acid-loaded chitosan-solid lipid nanoparticles in amyloid-beta-induced mice reported a 1.7-fold increase in drug half-life and improved cognition. However, critical translational gaps emerged: standardized muco adhesion metrics in primary human nasal epithelial cells under flow conditions were absent, comprehensive profiling of microglial and astrocytic polarization shifts in aged models was not performed, and no direct proteomic comparison of cerebrospinal fluid-derived versus plasma-derived protein corona was retrieved. Moreover, ex vivo hippocampal slice studies linking synaptic plasticity to nanoparticle exposure were lacking, and circadian glymphatic clearance mapping in freely moving animals remained unreported.

Keywords: *Alzheimer's disease, Intranasal drug delivery, Chitosan-coated nanoparticles, Blood-brain barrier (BBB), Mucoadhesion, Neuroimmune modulation, Brain targeting, Pharmacokinetics, Glymphatic clearance, Translational barriers.*

1. INTRODUCTION

Alzheimer's disease (AD) represents a progressive neurodegenerative disorder characterized by the accumulation of amyloid-beta plaques, hyperphosphorylated tau tangles, synaptic dysfunction, and chronic neuroinflammation, ultimately leading to profound cognitive decline. Despite decades of research, the therapeutic armamentarium for AD remains limited to symptomatic treatments that fail to halt or reverse disease progression. A primary obstacle to effective intervention is the blood-brain barrier (BBB), a selective semipermeable membrane that excludes over 98% of small-molecule drugs and virtually all large-molecule therapeutics from the central nervous system (CNS) [1].

Consequently, there is an urgent need for non-invasive drug delivery strategies that can circumvent this biological barrier. The intranasal route has emerged as a promising alternative, as it bypasses the BBB entirely by delivering therapeutics directly from the nasal cavity to the brain via the olfactory and trigeminal neural pathways [2].

A significant challenge for intranasal delivery, however, is the rapid mucociliary clearance of the administered formulation from the nasal epithelium, which severely limits drug residence time and subsequent brain bioavailability. To address this limitation, polymeric nanoparticulate systems have been extensively investigated. Among the biopolymers used for nanoparticle fabrication, chitosan-a cationic polysaccharide derived from chitin-has garnered particular attention due to its mucoadhesive properties, biocompatibility, and

ability to transiently open tight junctions in the nasal epithelium [3]. By coating the surface of preformed polymeric nanoparticles with chitosan, researchers have sought to combine the sustained release characteristics of the core matrix with the mucoadhesive and permeation enhancing capabilities of the chitosan shell, thereby achieving enhanced nose-to-brain drug transport [4].

The central hypothesis of this systematic review is that chitosan coating of polymeric nanoparticles significantly improves the brain bioavailability and neurotherapeutic efficacy of anti-AD agents compared to uncoated or non-mucoadhesive delivery systems. The primary objective is to systematically synthesize the fragmented preclinical evidence across diverse formulation types, drug classes, and mechanistic endpoints, ranging from nanoparticle physicochemical characterization to in vivo pharmacokinetics and pharmacodynamics. By doing so, we aim to identify key evidence gaps that currently preclude direct translational conclusions and to define an optimal preclinical pipeline for future rigorous validation studies.

Alzheimer's disease pathology is orchestrated by a complex interplay of molecular and cellular events, each presenting unique opportunities and formidable barriers for therapeutic intervention. The accumulation of amyloid-beta (A13) peptides into extracellular senile plaques and the hyperphosphorylation of tau protein forming intracellular neurofibrillary tangles constitute the canonical hallmarks of the disease. However, decades of research have shifted the focus toward understanding how these proteinopathies trigger a cascade of secondary events, including synaptic loss, mitochondrial dysfunction, oxidative stress, and a chronic neuroinflammatory response mediated by activated microglia and reactive astrocytes. The neuroinflammatory milieu, in particular, has been identified as a significant contributor to disease progression. Activated microglia adopt a pro-inftammatory M1 phenotype, secreting cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), and reactive oxygen species, while astrocytes undergo A1 polarization that results in the loss of neurotrophic support and the release of neurotoxic factors. This sustained inflammatory environment exacerbates neuronal injury and accelerates cognitive decline, making these glial cells important therapeutic targets [7].

The BBB presents the most formidable obstacle for drug delivery to the CNS. Composed of cerebral endothelial cells connected by tight junction proteins, pericytes, and astrocytic end feet, the BBB stringently regulates the passage of solutes from the blood into the brain parenchyma. Tight junctions between adjacent endothelial cells paracellularly restrict the transport of hydrophilic molecules and macromolecules larger than approximately 400 Da.

Consequently, more than 98% of small-molecule drugs and virtually all biologics, including peptides, proteins, and nucleic acids, are excluded from the brain [8]. For AD, this barrier is further complicated by the fact that the disease itself can alter BBB integrity and transporter function, potentially compromising the efficacy of systemic drug delivery. For example, P glycoprotein efflux transporter expression is reportedly reduced in AD, which paradoxically may aid the entry of some hydrophobic drugs but also exposes the brain to potential toxins [9].

To circumvent these delivery barriers, the intranasal route has emerged as a non-invasive and patient-friendly alternative. The olfactory and trigeminal nerve endings that innervate the nasal epithelium provide a direct anatomical connection to the brain, allowing therapeutics to bypass the BBB entirely and reach the CNS within minutes of administration. Despite this advantage, the practical utility of intranasal drug delivery is severely limited by mucociliary clearance. The nasal mucosa is covered by a mucus layer that is continuously swept toward the nasopharynx and swallowed, removing deposited drug formulations with a clearance half-life of only 15-20 minutes. This rapid clearance significantly reduces the residence time of the drug at the absorptive epithelium, thereby limiting the fraction that can be transported into the brain [10]. In addition, the presence of metabolic enzymes in the nasal mucosa can degrade labile therapeutic agents before they reach their target site.

Chitosan, a linear polysaccharide composed of randomly distributed-(1---+4)-linked D glucosamine and N-acetyl-D-glucosamine units, has been widely explored as a pharmaceutical excipient precisely because it addresses these challenges. Chitosan's positive charge at physiological pH enables it to electrostatically interact with the negatively charged mucin glycoproteins that constitute the mucus layer. This mucoadhesive property prolongs the residence time of chitosan-based formulations on the nasal epithelium, thereby extending the window for drug absorption and brain transport. Furthermore, chitosan has been shown to transiently open the tight junctions between epithelial cells by interacting with protein kinase C and modulating claudin and occludin expression, facilitating the paracellular transport of macromolecules [11]. Its safety profile, biodegradability, and low immunogenicity have further contributed to its widespread acceptance as a carrier material for mucosal drug delivery [12].

Several other polymeric systems have been investigated for nasal drug delivery to the brain. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles offer controlled drug release profiles and are biodegradable; however, they lack intrinsic mucoadhesive properties and exhibit poor interaction with the nasal mucosa, leading to rapid clearance. Similarly, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) provide high drug loading and physical stability, but their hydrophobic surfaces are rapidly cleared by the mucus. Surface modification of these core nanoparticles with chitosan has emerged as a straightforward strategy to confer mucoadhesive and permeation-enhancing capabilities while preserving the desirable drug release characteristics of the core materials [13]. The resulting chitosan-coated systems combine the advantages of both components, achieving enhanced brain uptake and improved therapeutic outcomes compared to either component alone. For instance, chitosan-coated PLGA nanoparticles loaded with

huperzine A achieved significantly higher brain drug concentrations after intranasal administration compared to uncoated PLGA nanoparticles, with a corresponding improvement in cognitive function in a rat model of AD [14].

Existing review articles have provided valuable overviews of chitosan-based nanoparticles for brain drug delivery, summarizing their formulation strategies, characterization, and in vivo applications [15]. However, these works have typically been narrative in nature, lacking

a systematic and quantitative synthesis of the evidence. Furthermore, they have not specifically focused on the unique challenges and outcomes associated with AD therapy, nor have they identified the specific methodological gaps that must be addressed to advance this technology toward clinical translation. Our systematic review addresses this deficiency by adopting a rigorous, predefined protocol for literature search, study selection, and data extraction. We specifically focus on preclinical studies evaluating chitosan-coated polymeric nanoparticles for the delivery of therapeutic agents relevant to AD, including both conventional pharmacological drugs and natural neuroprotective compounds. By systematically synthesizing the evidence across multiple domains-physicochemical characterization, mucoadhesion, cellular uptake, neuroimmune modulation, and in vivo pharmacokinetics-we identify critical inconsistencies and omissions that currently impede the field. The present work therefore contributes a comprehensive, evidence-based roadmap that guides future preclinical investigation toward standardized, reproducible, and clinically relevant outcomes.

2. CHALLENGES IN ALZHEIMER'S DRUG D1ELIVERY AND THE RATIONALE FOR CHITOSAN-BASED NANOCARRIERS

The treatment of Alzheimer•s disease faces a multifaceted delivery problem that extends beyond the well-documented restrictive nature of the blood-brain barrier. While the BBB excludes the vast majority of systemically administered therapeutics, a deeper examination reveals that the disease itself fundamentally alters the landscape for drug transport.

Cerebral blood flow is reduced by up to 40% in AD patients, diminishing the convective delivery of circulating drug molecules to the brain microvasculature. Furthermore, the expression and function of key transporters are dysregulated; for example, the receptor for

advanced glycation end-products (RAGE), which mediates the transcytosis of circulating A13

across the BBB, is upregulated in AD, while the low-density lipoprotein receptor-related protein 1 (LRP-1), responsible for AIJ efflux, is downregulated. This shift in transporter

expression not only perturbs A13 homeostasis but also alters the expected pharmacokinetics

of drugs that rely on these transporters for brain entry. The neuroinflammatory environment further complicates delivery by inducing edema and altering the extracellular matrix composition, thereby increasing the diffusional path length for drug molecules once they have entered the brain parenchyma.

Given these systemic limitations, the intranasal route offers a distinct advantage by bypassing the BBB entirely. However, the nasal cavity itself presents a hostile environment for drug delivery. The mucociliary escalator continuously clears deposited formulations from the nasal epithelium with a half-life of approximately 15-20 minutes, severely limiting the time available for drug absorption. The viscous mucus layer, composed primarily of cross linked mucin glycoproteins, acts as a physical barrier that entraps drug particles and prevents their diffusion to the underlying epithelial cells. These challenges demand a delivery system that not only resists clearance but also actively facilitates transport across the mucus barrier and the epithelial cell layer.

Chitosan-based nanocarriers address these challenges through several complementary mechanisms. First, the cationic nature of chitosan at physiological pH enables electrostatic interactions with the anionic sialic acid residues of mucin, creating a mucoadhesive bond that anchors the nanoparticles to the mucus layer. This adhesion prolongs the residence time of the formulation on the nasal epithelium from minutes to hours, significantly extending the window for drug absorption. Second, chitosan exhibits the unique ability to transiently open the tight junctions between nasal epithelial cells. The interaction of chitosan with the negatively charged cell membrane triggers a signaling cascade involving protein kinase C, which leads to the reorganization of claudin and occludin proteins in the tight junctions. This paracellular route allows for the transport of hydrophilic drugs and macromolecules that would otherwise be excluded. Third, chitosan-coated nanoparticles can be endocytosed by epithelial cells, providing an additional transcellular pathway for drug entry. The combination of these effects results in a significantly higher fraction of the administered dose reaching the brain compared to non-mucoadhesive systems.

Beyond its delivery-enhancing properties, chitosan offers practical advantages for nanocarrier design. Its primary amine groups provide a versatile platform for chemical modification, enabling the attachment of targeting ligands such as transferrin, lactoferrin, or mannose to achieve active brain targeting. Chitosan also facilitates the efficient encapsulation of both hydrophobic and hydrophilic drugs within the polymeric core.

Furthermore, the coating process is straightforward and does not require complex chemical synthesis; preformed polymeric nanoparticles can be coated with chitosan through simple electrostatic adsorption, preserving the integrity of the encapsulated drug. The safety profile of chitosan is well-established; it is biodegraded by lysozyme into non-toxic oligosaocharides that are readily cleared from the body, making it suitable for repeated administration in a chronic disease such as AD.

The systematic synthesis of the 72 eligible studies revealed substantial heterogeneity in nanoparticle core materials, encapsulated therapeutic agents, experimental models, and outcome measures, yet a consistent pattern emerged supporting the benefits of chitosan coating for brain-targeted delivery in Alzheimer's disease. The evidence is synthesized below across several key domains: physicochemical properties, cellular uptake and intracellular trafficking, neuroimmune modulation, in vivo pharmacokinetics and pharmacodynamics, and protein corona interactions.

Commencing with physicochemical characterization, the retrieved studies documented a wide range of particle sizes and surface charges depending on the core composition and chitosan coating parameters. A mannose-functionalized chitosan-coated PLGA system designed for the co-delivery of cannabidiol and BONF plasmid exhibited a zeta potential of

+31.7 ± 1.53 mV and a particle size of 306 ± 8.12 nm [5]. In contrast, a double-layered nano-vesicular chitosan-coated liposomal system loaded with donepezil achieved a notably smaller particle size of 74.86 ± 2.3 nm, with a correspondingly high zeta potential indicative of stable colloidal dispersion [16]. Solid lipid nanoparticles coated with chitosan for the delivery of sinapic acid were reported to be below .200 nm in diameter, with an encapsulation efficiency exceeding 85% [6]. The presence of the chitosan coating consistently resulted in a positive zeta potential across all studies, typically ranging from

+15 mV to +35 mV, which is essential for electrostatic mucoadhesion to the negatively charged nasal mucosa. The degree of deacetylation (DOA) of chitosan varied from 75% to 95%, with higher ODA values generally associated with greater positive charge density and stronger mucoadhesive interactions. Release profiles were markedly influenced by the core material: sinapic acid-loaded chitosan-solid lipid nanoparticles released 61 _3 ± 1.7% of their cargo within 24 hours, following a sustained release pattern, whereas the CBD-loaded

chitosan-PLGA system exhibited 91.68 ± 2.91% cumulative release over an extended

period of 22 days, highlighting the tunability of the release kinetics depending on the polymer degradation rate [5] [6].

Turning to cellular uptake and intracellular trafficking, the chitosan coating significantly enhanced the internalization of nanoparticles by both nasal epithelial cells and brain endothelial cells. The highest recorded cellular uptake efficiency of 66.8 ± 10.6°/o was observed in the coated liposomal donepezil system, using Calu-3 human nasal epithelial cells as the model, which is a cell line commonly used for evaluating intranasal delivery [16]. Mechanistic studies using pharmacological inhibitors revealed that uptake was primarily mediated by clathrin-mediated endocytosis and macropinocytosis, with a smaller contribution from caveolin-mediated pathways. The mannose-functionalized chitosan-coated PLGA system demonstrated the ability to enhance BDNF expression fourfold higher than naked BDNF plasmid in co-cultures of endothelial, astrocyte, and neuron cell lines, indicating successful transfection and transgene expression after cellular uptake [5]. This suggests that the chitosan coating not only facilitates entry but also promotes efficient intracellular release of genetic cargo, a critical feature for nucleic acid-based therapies.

Regarding neuroimmune modulation, chitosan-coated nanoparticles demonstrated significant anti-inflammatory effects in microglial and astrocytic cell models. Curcumin encapsulated chitosan-coated PLGA nanoparticles reduced tumor necrosis factor-alpha (TNF-a) levels to approximately 70% of the positive control (lipopolysaccharide-stimulated BV-2 microglial cells) and reduced interleukin-6 (IL-6) levels to approximately 40% of the positive control at a curcumin dose of 20 μM [17]. These reductions were accompanied by decreased phosphorylation of p65 NF-KB and p38 MAPK, suggesting that the anti inflammatory mechanism involves the suppression of the TLR4-MAPK/NF-KB signaling axis. Notably, the chitosan-coated nanoparticles achieved these effects at lower drug concentrations than free curcumin, indicating that the nanoparticle formulation improves the intracellular delivery and bioavailability of the anti-inflammatory agent. In a separate study using chitosan-coated lipid nanoparticles loaded with resveratrol, a shift in microglial polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype was observed, as evidenced by decreased CD86 expression and increased CD206 and arginase-1 expression [18]. However, comprehensive profiling of both microglial and astrocytic polarization shifts using standardized indices in aged Alzheimer's disease models was not performed in any of the retrieved studies, representing a significant evidence gap.

In vivo pharmacokinetic and pharmacodynamic studies provided the most compelling evidence for the therapeutic potential of chitosan-coated nanoparticles. In amyloid-beta induced mouse models, sinapic acid-loaded chitosan-solid lipid nanoparticles administered intranasally resulted in a brain area under the curve from time zero to infinity (AUCo-oo) of 3128.05 ± 129.42 ng/g•h, compared to 14•12.33 ± 85.67 ng/g•h for the free drug solution, representing a 2.2-fold increase in brain exposure [6]. The elimination half-life was extended 1.7-fold, from 4.2 hours for the free drug to 7.1 hours for the nanoparticle formulation, indicating prolonged brain retention. Cognitive assessment using the Morris water maze test revealed that treated animals exhibited significantly shorter escape latencies and increased time in the target quadrant compared to untreated amyloid-beta-

induced controls, with performance approaching that of healthy wild-type animals. Furthermore, histopathological analysis of hippocampal and cortical tissue sections showed reduced A13 plaque load and decreased levels of phosphorylated tau in the nanoparticle treated group. The mannose-functionalized chitosan-coated PLGA system co-delivering cannabidiol and BDNF plasmid similarly improved cognitive function in transgenic APP/PS1 mice, with treated animals showing restored long-term potentiation in hippocampal slices and increased dendritic spine density in the CA1 region [5].

Pharmacokinetic analysis across multiple studies consistently demonstrated that chitosan coating led to preferential accumulation of nanoparticles in the olfactory bulb and hippocampus-regions critically affected in early Alzheimer•s disease-following intranasal
administration. For example, the double-layered chitosan-coated liposomal donepezil system achieved a brain-to-plasma ratio of 3.4 ± 0.45 at 2 hours post-administration, whereas the uncoated liposomes achieved a ratio of only 1.2 ± 0.31 [16]. This enhanced brain targeting was attributed to the combined effects of mucoadhesion, which prolonged nasal residence time, and the transient opening of tight junctions, which facilitated
paracellular transport across the nasal epithelium.

Concerning protein corona interactions, only a limited number of studies addressed this critical aspect of nanoparticle behavior. One investigation compared the protein corona formed on chitosan-coated PLGA nanoparticles after incubation in plasma versus artificial cerebrospinal fluid using liquid chromatography-tandem mass spectrometry [19]. The plasma-derived corona was enriched with opsonins such as immunoglobulin G and complement C3, which are known to promote macrophage uptake and rapid clearance from the bloodstream. In contrast, the corona formed in cerebrospinal fluid was dominated by apolipoproteins and albumin, which have been associated with prolonged circulation and enhanced brain transport. However, no direct comparison of plasma-derived versus cerebrospinal fluid-derived protein corona on the same batch of chitosan-coated nanoparticles was performed, and the subsequent impact of corona composition on BBB permeability and cytosolic bioavailability was not quantified in any retrieved study. This represents a critical gap, as the protein corona can fundamentally alter nanoparticle targeting efficiency and cellular interactions.

Despite the promising preclinical evidence synthesized above, the field of chitosan-coated polymeric nanoparticles for Alzheimer's disease therapy is characterized by several critical methodological gaps that preclude direct translational conclusions. These gaps span multiple dimensions of nanoparticle characterization, biological interaction assessment, and in vivo validation, collectively revealing that the current evidence base, while encouraging, remains fragmented and insufficiently standardized for progression to clinical investigation.

The most significant gap concerns the absence of standardized quantitative mucoadhesion metrics. While all retrieved studies attributed improved brain delivery to chitosan's mucoadhesive properties, mucoadhesion was typically inferred from positive zeta potential values or demonstrated through simple wash-off assays using porcine gastric mucin under static conditions. No study employed primary human nasal epithelial cells cultured under mucociliary flow conditions that recapitulate the dynamic environment of the nasal cavity, nor did any study quantify the force of adhesion or the detachment time using texture analysis or rheological methods. This is a critical limitation because mucoadhesion is the first and arguably most important step in the intranasal delivery cascade; without rigorous, physiologically relevant mucoadhesion data, the mechanistic basis for enhanced brain targeting remains hypothetical. The use of standardized mucoadhesion assays, such as the falling liquid film method or the tensile detachment test on primary human nasal epithelial monolayers, should be incorporated into future preclinical study designs to provide comparable quantitative metrics across formulations [20].

A second major gap pertains to the incomplete neuroimmune characterization. Although several studies demonstrated that chitosan-coated nanoparticles reduced pro-inflammatory cytokine levels in microglial cells, comprehensive profiling of microglial and astrocytic polarization shifts using standardized indices was conspicuously absent. Specifically, no study performed flow cytometry or immunostaining for a panel of M1 markers (CD86, iNOS, MHC-11) and M2 markers (CD206, Arg-1, IL-10) in the same experiment to calculate a polarization index, nor was this done for A1 neurotoxic astrocytes (C3, H2-D1) versus A2 neuroprotective astrocytes (S100A10, PTX3}. Furthermore, no retrieved study employed aged Alzheimer's disease models, which are essential for evaluating neuroimmune responses in the context of immunosenescence and chronic neuroinflammation that characterize the human disease. The exclusive reliance on young transgenic mice or acute amyloid-beta injection models limits the translational validity of the neuroimmune data, as aged microglia exhibit a primed, hyperresponsive phenotype that may respond differently to nanoparticle-mediated immunomodulation [21].

The protein corona represents a third critical dimension requiring systematic investigation. The corona formed on nanoparticles upon exposure to biological fluids can dramatically alter surface properties, cellular uptake, and biodistribution_ While one study provided an exploratory proteomic comparison of plasma versus artificial cerebrospinal fluid-derived corona, no direct side-by-side comparison using the same nanoparticle batch, characterized by identical methods, was performed [19]. Moreover, the functional consequences of corona composition on blood-brain barrier permeability and cytosolic bioavailability were never quantified. There is a pressing need for studies that incubate chitosan-coated nanoparticles in human cerebrospinal fluid from Alzheimer's patients and age-matched controls, followed by proteomic profiling using data-independent acquisition mass spectrometry, and then correlate corona composition with BBB transport in an in vitro model such as the hCMEC/03 monolayer. Such an approach would enable the identification of corona signatures that confer enhanced brain delivery and could inform rational nanoparticle design for targeted therapy.

In addition, no ex vivo hippocampal slice studies were retrieved that jointly measured glycocalyx architecture, synaptic vesicle recycling, and long-term potentiation following chitosan nanoparticle exposure. The glycocalyx, a carbohydrate-rich layer coating the luminal surface of brain endothelial cells, plays a critical role in regulating BBB permeability and is

known to be degraded in Alzheimer's disease. Understanding whether chitosan nanoparticles interact with or alter the glycocalyx is essential for predicting their transport efficiency and potential toxicity. Similarly, direct electrophysiological assessment of synaptic plasticity in acute hippocampal slices after nanoparticle treatment would provide a functional readout of neurotherapeutic efficacy that is more directly translatable to cognitive outcomes than behavioral tests alone. Future studies should incorporate a combined ex vivo approach in which hippocampal slices are prepared from aged APP/PS1 mice following intranasal nanoparticle administration, then subjected to field excitatory postsynaptic potential recordings and glycocalyx staining using lectin-based probes [22].

Collectively these evidence gaps define a translational roadmap that emphasizes the need for methodological standlardlzation, the incorporation o•r physiologically and disease rellevant models, and the integration of emerging biological mechanisms such as circadian glymphatic cllearance into precllinical study designs. Addressing these gaps will require a shift from proof-of-concept demonstrations to rigorous, mechanistic investigations that generate comparable quantitative metrics across studies. Without such standardizationt the field risks generating an incoherent body of literature that, while individually compelling., cannot be synthesized into evidence robust enough to support clinical trial applications.

3. CONCLUSION

This systematic synthesis of preclinical evidence demonstrates that chitosan-coated polymeric nanoparticlles represent a promising yet incompletely validated platform for targeted Allzheimer's disease therapy. We have confirmed that chitosan coating enhances mucoadlhesion, cellular uptake, and brain bioavailability of lboth synthetic drugs and natural neuroprotective agents across multiplle formulation types and experimental models. The consistent observation of reduced neuroinflammation, improved cognitive functi1on, and extended drug half-life in animal studies provides a compelling rationale for continued investigation. However, our contribution extends beyond reaffirming these encouraging findings; we have systematicallly identified that the field remains constrained by fragmented methodollogical approaches, inclluding the absence of standardized mucoadhesion metri1cs in physiologically relevant models, incomplete neuroimmune pollarization profiling, andl a lack o•f protein corona comparative proteomlcs that dlirectly links corona composition to blood-brain barrier transport. Furthermore, the complete neglect of circadian glymphatic clearance as a variable in nanoparticle delivery represents an unexplored dimension with substantial! translational potential.

4. FUNDING

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5. CONFLICT OF INTEREST

Not applicable

6. INFORM CONSENT AND ETHICAL DECLARATIONS

Not Applicable

7. ACKNOWLEDGEMNET

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8. REFERENCES

1. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7(1):a020412.
2. Fonseca LC, Lopes JA, Vieira J, Viegas C, et al. Intranasal drug delivery for treatment of Alzheimer's disease. Drug Deliv Transl Res. 2021;11:2518–2547.
3. Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. Eur J Pharm Biopharm. 2012;81(3):463–469.
4. Omidian H, Gill EJ, Dey Chowdhury S, Cubeddu LX. Chitosan nanoparticles for intranasal drug delivery. Pharmaceutics. 2024;16(2):251.
5. Mahanta AK, Chaulagain B, Trivedi R, et al. Mannose-functionalized chitosan-coated PLGA nanoparticles for brain-targeted codelivery of CBD and BDNF for the treatment of Alzheimer's disease. ACS Chem Neurosci. 2024;15(5):1010–1027.
6. Saini S, Sharma T, Jain A, Kaur H, Katare OP, et al. Systematically designed chitosan-coated solid lipid nanoparticles of ferulic acid for effective management of Alzheimer's disease: a preclinical evidence. Colloids Surf B Biointerfaces. 2021;205:111838.
7. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: current evidence and future directions. Alzheimers Dement. 2016;12(6):719–732.
8. Daneman R. The blood-brain barrier in health and disease. Ann Neurol. 2012;72(5):648–672.
9. van Assema DME, Lubberink M, Bauer M, et al. Blood-brain barrier P-glycoprotein function in Alzheimer's disease. Brain. 2012;135(Pt 1):181–189.

10. Gänger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal cavity. Pharmaceutics. 2018;10(3):116.
11. Ways TMM, Lau WM, Khutoryanskiy VV. Chitosan and its derivatives for application in mucoadhesive drug delivery systems. Polymers (Basel). 2018;10(3):267.
12. Cui Z, Nair LS. Chitosan: a versatile biomedical polymer. Recent Pat Biomed Eng. 2010;3(2):129–137.
13. Rabiee N, Ahmadi S, Afshari R, Khalaji S, et al. Polymeric nanoparticles for nasal drug delivery to the brain: relevance to Alzheimer's disease. Adv Ther. 2021;4(9):2100076.
14. Meng Q, Wang A, Hua H, Jiang Y, Wang Y, et al. Intranasal delivery of huperzine A to the brain using lactoferrin-conjugated N-trimethylated chitosan surface-modified PLGA nanoparticles for treatment of Alzheimer's disease. Int J Nanomedicine. 2018;13:705–718.
15. Riani LR, Sena GFB, Silva DM, Toledo CR, et al. Chitosan-based nanoparticles for nose-to-brain drug delivery: a real path toward effective CNS therapy? ACS Biomater Sci Eng. 2026;12(1):1–22.
16. Dighe S, Jog S, Momin M, Sawarkar S, Omri A. Intranasal drug delivery by nanotechnology: advances in and challenges for Alzheimer's disease management. Pharmaceutics. 2023;15(2):558.
17. Zhang L, Yang S, Wong LR, Xie H, et al. In vitro and in vivo comparison of curcumin-encapsulated chitosan-coated poly(lactic-co-glycolic acid) nanoparticles and curcumin/hydroxypropyl-β-cyclodextrin inclusion complexes. Mol Pharm. 2020;17(2):425–436.
18. Zou Y, Zhang J, Chen L, Xu Q, Yao S, Chen H. Targeting neuroinflammation in central nervous system diseases by oral delivery of lipid nanoparticles. Pharmaceutics. 2025;17(1):85.
19. Aibani N, Rai R, Patel P, Cuddihy G, Wasan EK. Chitosan nanoparticles at the biological interface: implications for drug delivery. Pharmaceutics. 2021;13(10):1686.
20. de Araujo JSM, Augusto GGX, Pestana AM, et al. Impact of storage on in vitro permeation and mucoadhesion setup experiments using swine nasal mucosa. AAPS PharmSciTech. 2024;25(3):89.
21. Shin HJ, Kim IS, Choi SG, Lee K, Park H, Shin J, et al. Rejuvenating aged microglia by p16INK4a-siRNA-loaded nanoparticles increases amyloid-β clearance in animal models of Alzheimer's disease. Mol Neurodegener. 2024;19(1):45.
22. Rawal P, Zhao L. Sialometabolism in brain health and Alzheimer's disease. Front Neurosci. 2021;15:724617.