Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 1220-1236
DoI-10.004687/1000-9035.2025.164

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Intranasal In-Situ Gel Systems as Smart Nose-to-Brain Drug Delivery Platforms for Alzheimer's Disease: Mechanistic Insights, Nanotechnological Advances, and Translational Prospects.

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Article Information
Received: 25-11-2025
Revised: 02-12-2025
Accepted: 05-12-2025
Published: 15-12-2025

Keywords
Alzheimer's disease, intranasal drug delivery, in-situ gel, nose-to-brain transport, mucoadhesive polymers, and nanotechnology.

ABSTRACT
Alzheimer's disease (AD) is the most common neurodegenerative disorder worldwide, characterised by progressive loss of memory and cognitive functions. The conventional oral and parenteral therapies for AD suffer from several critical limitations arising from poor permeability across the blood-brain barrier (BBB), systemic toxicity, and rapid degradation of the drugs. In this context, intranasal *in-situ* gel drug delivery systems have emerged as a very attractive non-invasive approach, offering direct nose-to-brain transport with sustained release, enhanced bioavailability, and improving patient compliance. Such systems integrate mucoadhesive polymers of distinct functionalities, such as chitosan, gellan gum, and poloxamers, with stimuli-responsive sol-gel transitions to prolong nasal residence time and optimize absorption through olfactory and trigeminal pathways. In this regard, recent preclinical studies, such as donepezil-loaded bovine serum albumin nanoparticles incorporated in thermosensitive gels, and lutein-loaded in-situ gels, revealed significant enhancement in brain drug concentration and neuroprotective efficacy compared to the conventional routes of drug delivery. More recently, continuous development in the fields of nanoparticle-embedded gels and cubosomal formulations has further improved the stability and targeted delivery of synthetic and phytochemical therapeutics. Despite encouraging findings, certain challenges, such as mucociliary clearance and long-term nasal toxicity and formulation reproducibility, remain. This review summarizes recent innovations, mechanistic insights, and translational progress of intranasal in-situ gel systems in AD therapy that have bridged the pharmacological gap between systemic administration and efficient CNS targeting of therapeutics. These intranasal in situ gel platforms represent a transformative strategy for the effective management of Alzheimer's disease through the integration of various emerging polymer science and nanotechnology.

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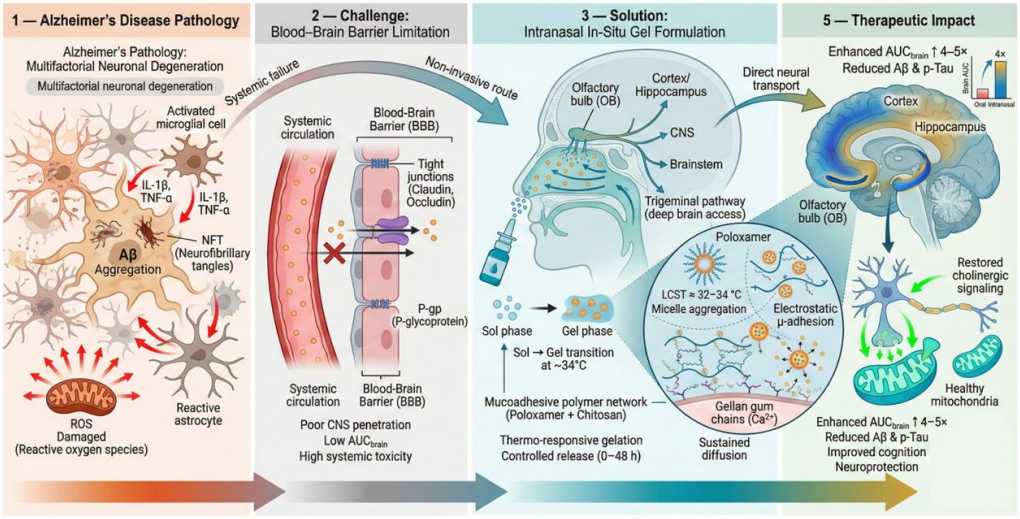
Graphical Abstract



1. INTRODUCTION:

Alzheimer's disease represents one of the most devastating neurodegenerative disorders of the 21st century, consisting of progressive cognitive decline with memory loss and death of neurons[1]. It has been estimated to cause almost 60-70% of dementia throughout the world, while its incidence is likely to triple by the year 2050 on account of the increasing ratio of aged populations globally[2]. Even after immense research for decades, the therapeutic horizon of AD remains confined because its multifactorial pathophysiology includes Aβ aggregation, tau hyperphosphorylation[3], oxidative stress, mitochondrial dysfunction, and neuroinflammation. Presently, available drugs, basically acetylcholinesterase inhibitors like donepezil and NMDA receptor antagonists such as memantine, facilitate symptomatic relief without modifying the progression of the disease. The basic challenge lies in achieving enough concentration of the therapeutic agent to reach the brain and, at the same time, overcoming the restrictive nature of the BBB[4].

The BBB indeed presents one of the biggest challenges when it comes to systemic drug delivery for neurotherapeutics. Composed of tightly joined endothelial cells, astrocytic end-feet, and pericytes, this barrier allows few small lipophilic compounds while excluding most hydrophilic compounds and large molecules (>400 Da)[5]. This stromal-like physical barrier highly restricts the entry of neuroprotective peptides, proteins, and nucleic acid-based drugs into the brain parenchyma. Conventional oral and parenteral routes, therefore, fail to achieve effective brain bioavailability[6]. Moreover, hepatic first-pass metabolism and peripheral side effects further compromise therapeutic outcomes. Limitations such as these have driven the search for unconventional routes and formulations that enable direct brain targeting with improved patient compliance[7].

In situ gels are a class of polymer solutions which can undergo a sol-to-gel transition on exposure to external stimuli such as temperature, pH, and ionic strength. In a nasal delivery system, thermresponsive in situ gelling systems based on polymers such as poloxamer 407, chitosan, and carbopol show mucoadhesive properties and have a prolonged residence time in the nasal cavity, thus providing better absorption of drugs[8]. On being delivered intranasally, these systems can readily melt to form a liquid, which in turn can transform into a bioadhesive gel in response to interaction with the mucous lining in the nasal passages, thus providing sustained release with better permeability. Such delivery systems can prove very effective in chronic ailments such as Alzheimer's in which a constant level of drugs in the brain is required[9].

In recent years, in-situ gels have been successfully incorporated with nanotechnology carriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), cubosomes, and poly mercenaries. With these combinations, higher encapsulation capacity, resistance to degradation, and controlled release can be achieved[10]. On being

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delivered intranasally, these systems can readily melt to form a liquid, which in turn can transform into a bioadhesive gel in response to interaction with the mucous lining in the nasal passages, thus providing sustained release with better permeability. Such delivery systems can prove very effective in chronic ailments such as Alzheimer's in which a constant level of drugs in the brain is required[9].

On being delivered intranasally, these systems can readily melt to form a liquid, which in turn can transform into a bioadhesive gel in response to interaction with the mucous lining in the nasal passages, thus providing sustained release with better permeability. Such delivery systems can prove very effective in chronic ailments such as Alzheimer's in which a constant level of drugs in the brain is required [11] have successfully formulated felodipine-loaded in-situ gels using NLCs, which increased brain bioavailability in animal models of AD. Then enhanced donepezil delivery using bovine serum albumin nanoparticles incorporated into in-situ nasal gels. Moreover, terthys noted in a research article by that cubosomes can be used in thermoresponsive in-situ gels to effectively transport hydrophobic drugs across the olfactory epithelium[12].

With respect to pharmacokinetic considerations, intranasal in situ gels improve both regional brain concentration–time curve and AUC in brain tissues over plasma, indicating enhanced brain targeting efficacy for these formulations. A research in 2025 demonstrated a marked increase in AUC in the brain area after intranasal delivery of lutein-loaded *in situ* gels, thus validating these formulation's capability for nasal epithelium permeation and delivery to-target sites in the brain. Moreover, this delivery mode prevents exposure to systemic side effects, which is a very important consideration in elderly AD patients, especially taking into consideration their concomitant pharmacotherapy[12].

Biopharmaceutical issues, such as enzymatic degradation in the nasal passages, mucociliary transport, and stability of formulations, are being tackled by polymer engineering. For instance, chitosan increases paracellular permeability by temporarily disrupting tight junctions, with carbopol acting as a mechanical buttress and mucoadhesive. The addition of penetration enhancers, antioxidants, and surfactants serves to further improve drug delivery profiles. The biocompatibility and safety aspects of these polymers have been greatly proven in preclinical studies. Thorough integration of these breakthroughs brings a revolution in moving from conventional delivery systems to smart-responsive delivery systems specific to neurodegenerative diseases[13].

Clinically translated, intranasal in-situ gels reflect the increasing focus on patient-centric drug delivery systems. Their delivery formats, noninvasive nature, and less frequent dosing regimen can greatly promote patient compliance among senior patients. Nevertheless, a set of translational issues have yet to be addressed, such as physiological disparities among patients, interspecific anatomic differences among subjects, and a common model for evaluation. emphasized the usage of biologically relevant animal models and pharmacokinetic simulations to effectively forecast human results. Moreover, massive production, sterilization, and stability of these *in-situ* gel formulations need thorough research before gain-of-use application[14].

2. Pathophysiology and Current Therapeutic Limitations in Alzheimer's Disease:

2.1 Alzheimer's Disease:

AD is a multifactorial, progressive neurodegenerative disorder with prevalent memory loss, synaptic damage, and neuronal cell death, contributing to approximately 70% of all dementia incidence in the world. To date, despite numerous studies conducted over several decades, a complete understanding of pathogenesis in Alzheimer's disease remains unclear, rendering all treatment methods ineffective in slowing disease progression. The core pathological features in Alzheimer's disease include Aβ plaques in the extracellular space, intraneuronal tau protein neurofibrillary tangles (NFT) in the cytoplasm, neuroinflammations, and oxidative damage in neurons, which contribute to increased neuronal dysfunction and cognitive impairment in Alzheimer's patients[15].

2.2 Amyloid-β Aggregation and Neurotoxicity:

The amyloid cascade hypothesis, which dates to the 1990s, remains the cornerstone of pathophysiology in AD research. It hypothesizes that improper processing of amyloid precursor protein (APP) by β- and γ-secretases leads to an abundance of Aβ42, a hydrophobic peptide with a high risk of oligomerization. The Aβ oligomers affect synaptic function, suppress long-term potentiation, and initiate microglia-driven inflammatory reactions. Current research using advanced neuroimaging studies and analysis of cerebrospinal fluid markers continues to support that Aβ oligomers, rather than senile plaques, represent the major neurotoxic species in AD pathophysiology. Aβ oligomers affect neuronal calcium signaling pathways, cause mitochondrial damage, and initiate apoptosis through caspase activation. Aβ accumulation also

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influences vascular integrity. Experiments conducted utilizing blood-brain barrier (BBB) on a chip model indicated Aβ peptides to impact negatively on tight junctions of the endothelia and increase permeability, thus exacerbating neuroinflammation. Additionally, reduced clearance of Aβ in low-density lipoprotein receptor-related protein-1 (LRP1) and glymphatic systems leads to Aβ accumulation in the cerebral parenchyma and vasculature, resulting in cerebral amyloid angiopathy[16].

2.3 Hyperphosphorylation of Tau and Microtubule Destabilization:

Tau pathology is another important dimension of AD pathogenesis. Normally, tau prevents microtubule disintegration and participates in axonal transport. Uncontrolled kinase activation, such as glycogen synthase kinase 3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), results in hyperphosphorylation of tau, leading to its dissociation from microtubules and subsequent formation of paired helical filaments (PHFs). These inclusions cause derangement in cytoskeletal architecture in neurons and a failure in axonal transport of critical organelles and transmitters. Current proteomics research shows a prion-like model of tau pathology, where misfolded tau propagates trans-synaptically, leading to increased neurodegenerative responses in cortical and hippocampal connections . Moreover, tau pathology further worsens Aβ toxicity, thus creating a self-positive feedback loop leading to increased synaptic dysfunction and neuroinflammation [17].

2.4 Neuroinflammation and Glial Dysfunction:

Neuroinflammation has recently become established as a third major pathogenic factor in AD. Microglia/astrocyte activation in response to Aβ/tau aggregates leads to the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and reactive oxygen species (ROS). Neuroinflammation further promotes synaptic loss and neuronal apoptosis. Although microglia activation is a protective response for removing misfolded proteins, chronic microglia activation promotes a pathologic M1-like state driven by excessive production of nitric oxide and pro-inflammatory factors . A study conducted in 2025 by showed Aβ-tau co-pathology acts in a synergistic manner to activate NF-κB signaling, which in turn leads to microglial cell proliferation and neuroinflammation. Simultaneously, astrocytic dysregulation results in glutamate uptake abnormalities, calcium imbalance, and blood-brain barrier damage. Additionally, immune cell infiltration from the disrupted blood-brain barrier adds to neuroinflammation and thus an inflammatory cycle of neuronal death[18].

2.5 Oxidative Stress & Mitochondrial Damage:

The generation of reactive oxygen species (ROS) and mitochondrial dysfunction represent early components of AD pathogenesis. The resulting high oxidative load promotes lipid peroxidation, DNA damage, and protein oxidation, which affect neuronal function. Aβ aggregates interact with mitochondrial membranes, resulting in dysfunction of electron transport chain complexes and ATP depletion . Furthermore, hyperphosphorylated tau inhibits mitochondrial transport in axon pathways, which further contributes to ATP depletion in metabolically active neurons. Opening of mitochondrial permeability transition pores (mPTP), release of cytochrome c, and activation of intrinsic apoptotic pathways have all been evidenced in AD brains. Moreover, these oxidative modifications are inextricably entwined with neuroinflammation, where microglial activation acts as a further fuel for enhanced ROS production in a self-propagating pathophysiology loop[19].

2.6 Synaptic Abnormalities & Neurotransmitter Problems:

Aβ, tau, and inflammatory pathway accumulation culminates in marked synaptic dysfunction, which is the most reliable indicator of cognitive dysfunction in AD. There is a marked disruption in glutamergic and cholinergic transmission. Aβ oligomers affect NMDA receptor function, and tau dysfunction blocks neuronal vesicle transport of transmitters . Aβ oligomer functions have been linked to excitotoxicity and neuronal death. Reduced acetylcholine levels form the basis of present symptomatic management with cholinesterases[20].

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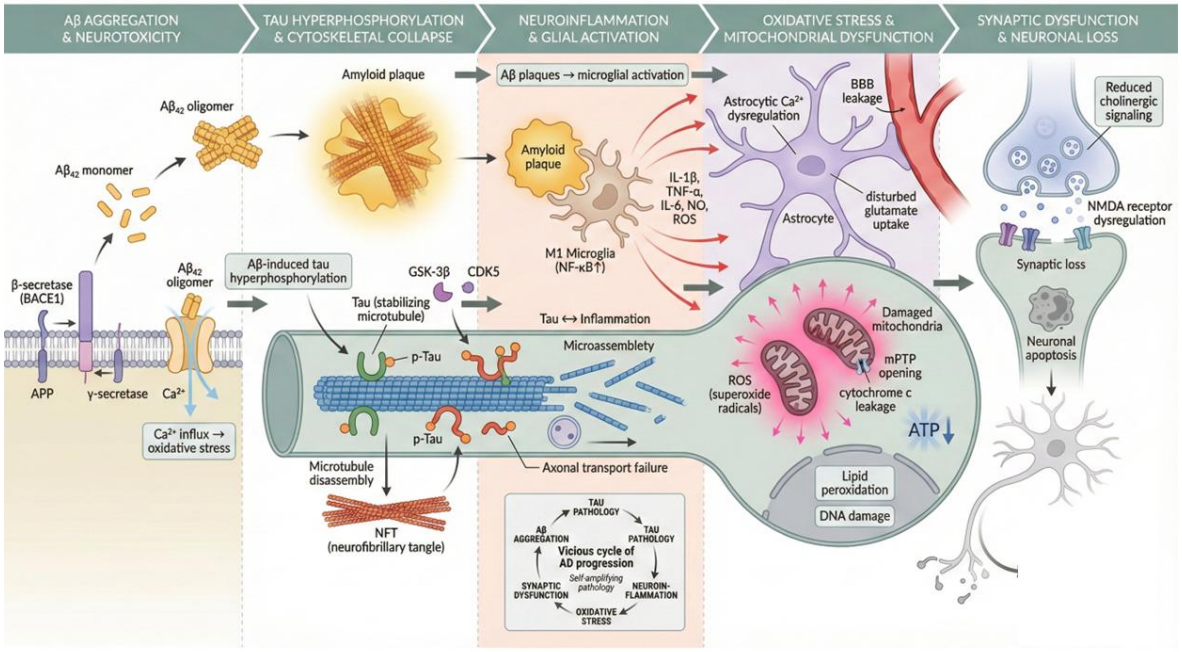

Figure 1 Molecular and Cellular Pathophysiology of Alzheimer's Disease: Interplay between Aβ Aggregation, Tau Hyperphosphorylation, Neuroinflammation, and Oxidative Stress.

3. Why Conventional Systemic Therapies Fail:

Although a lot of work has been conducted in this area, existing therapies for AD, such as donepezil, rivastigmine, galantamine, and memantine, provide only symptomatic relief without affecting the progression of the disease. Several pathophysiological and pharmacokinetic barriers are responsible for these impediments. The blood-brain barrier (BBB) is a major challenge in the delivery of therapeutic drugs into the systemic circulation. The BBB preferentially limits the passage of 98% of small molecules and all large biomolecules such as monoclonal antibodies and peptides into the central nervous system, thus hindering the CNS bioavailability of most drugs. In addition, efflux transporters such as P-glycoprotein and multidrug resistance proteins actively remove drugs from the brain parenchyma. Systemic drugs have poor pharmacokinetics, including substantial hepatic metabolism, poor stability in plasma, and non-specific distribution, resulting in poor concentrations in neurons . Therefore, higher doses are required, which predispose patients to gastrointestinal and cardiovascular side effects, especially in geriatric patients with comorbidities[21].

Monoclonal antibody therapies targeting Aβ, including lecanemab and donanemab, despite being approved recently, are associated with poor penetration across the BBB, high cost, and the possibility of Amyloid-Related Imaging Abnormalities (ARIA) side effect . Further, passive immunotherapy targeting tau proteins has proved disheartening in phase III trials because of poor CNS penetration with off-target toxicity. In addition, heterogeneity in diseases, which involves a combination of pathology related to both vascular and metabolic pathways, adds to treatment complexities. Also, a single pathway treatment will not be sufficient in dealing with a multifactorial pathophysiology of AD patients because of its complexity A combination of Aβ, tau, neuroinflammation, and oxidative stress pathways in AD patients will require a multi-target treatment approach with a BBB-penetrating The Need for Alternative Approaches to Delivery.[22]

The nine months Owing to issues associated with systemic delivery, nose-to-brain delivery of drugs, which circumvents the BBB and administers drugs targeted at the CNS through olfactory and trigeminal nerves, has gained prominence in recent studies. Of these delivery methods, intranasal in-situ gel systems have emerged as a sustained-release mucoadhesive delivery system with a potent potential for increasing residence time, absorption, and bioavailability of drugs with reduced systemic exposure, side effects, and applicability to both small molecules such as donepezil and memantine, and macromolecules such as peptides, siRNA, and nanoparticles for targeting the brain (23) .

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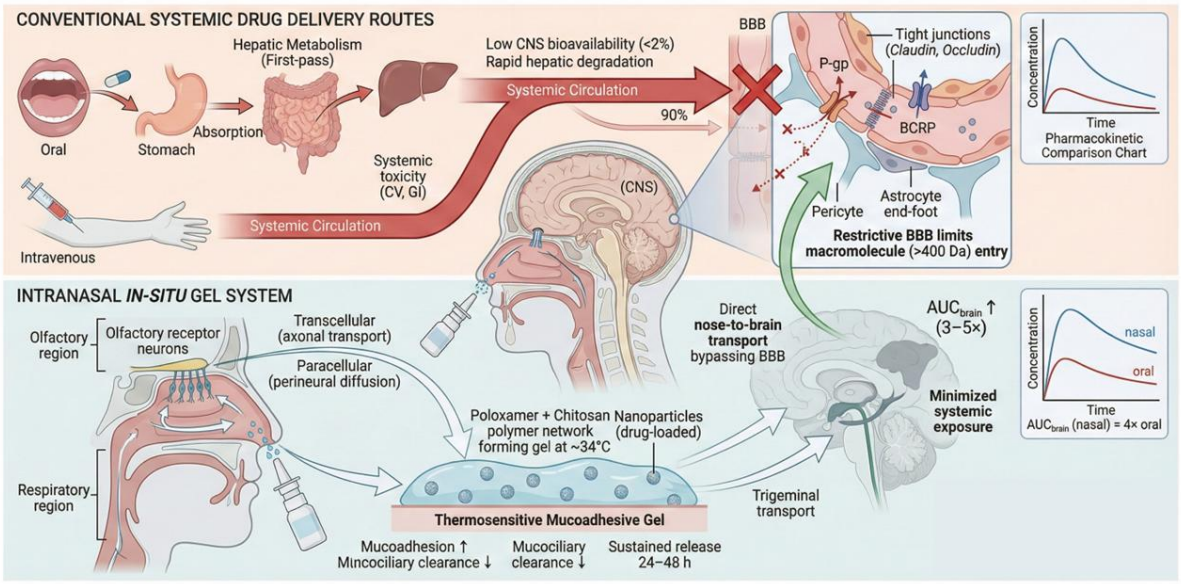

Figure 2 Challenges of Conventional Systemic Drug Delivery and the Advantages of Intranasal In-Situ Gels in Overcoming the Blood–Brain Barrier.

4. Intranasal Route as a Direct Nose-to-Brain Delivery Pathway:

The CNS remains a formidable challenge to therapeutic intervention because of its highly selective physiological interface, the BBB, which poses a formidable barrier to the passage of most drugs from systemic circulation into the brain. New delivery strategies that circumvent the BBB have therefore become imperative in neurotherapeutics. One of the most promising non-invasive methodologies of nose-to-brain transport is IN drug delivery, which can achieve high drug concentrations in target brain regions for both small and macromolecular drugs by this route. The unique anatomy and physiology of the nasal cavity, along with the existence of olfactory and trigeminal neural pathways, facilitate rapid and high-level transport of drugs to the brain while concurrently limiting systemic exposure[24].

4.1 Anatomical Basis of Intranasal Route:

The human nasal cavity is a respiratory and olfactory organ with an approximate surface area of 150–200 cm^2. It is divided by the nasal septum into two symmetrical halves and is composed of three main regions: the vestibular, respiratory, and olfactory regions. The respiratory region covers the largest surface area, with pseudostratified ciliated epithelium lined with goblet cells secreting mucus. This mucus layer works both as a physical barrier and a carrier, as it traps particulates while allowing drugs to diffuse across the epithelial membrane. The olfactory region, at the roof of the nasal cavity, comprises only approximately 8–10% of the total surface area but is the most significant site of nose-to-brain drug transport. It contains ORNs whose axons traverse the cribriform plate of the ethmoid bone directly into the olfactory bulb, offering a unique conduit between the external environment and the CNS. The nasal submucosa being highly vascularized allows for rapid systemic absorption of drugs. However, the key to CNS targeting is in the neural connection with the olfactory and trigeminal nerves in a way that bypasses the BBB, opening a route for direct access to the brain and CSF. The olfactory nerve route transports the drugs either intracellularly by axonal transport or extracellularly by perineural diffusion. However, a trigeminal pathway permits delivery to deeper brain structures such as the brain stem and cerebellum[25].

4.2 The Olfactory Pathway: A Gateway to the CNS:

The olfactory mucosa consists of a very specialized neuroepithelium made up of olfactory receptor neurons, supporting sustentacular cells, and basal stem cells. Two predominant mechanisms exist for the transport of drugs across the nasal mucosa after intranasal administration: transcellular (neuronal) and paracellular (extracellular) transport. In the case of the transcellular pathway, lipophilic molecules cross the olfactory neuronal membrane by means of endocytosis or passive diffusion, followed by axonal transport to the olfactory bulb. Although this process is relatively slow-on the order of hours-it facilitates the sustained delivery and localization of drugs to forebrain regions. The paracellular route involves extracellular diffusions of drugs along the perineural space surrounding the olfactory neurons. This route gives faster transport, often within minutes, to the olfactory bulb and other brain regions. Hydrophilic and macromolecular drugs, which normally are incapable of crossing the BBB, similarly benefited

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from this pathway when formulation with permeability enhancers includes but is not limited to chitosan or bile salts. Once drugs reach the olfactory bulb, they can diffuse further into cortical and limbic structures, including the hippocampus, amygdala, and prefrontal cortex-all of which are profoundly affected in AD[26].

4.3 Trigeminal Pathway: Drug Reach Beyond the Forebrain:

Along with the olfactory route, an equally crucial pathway for intranasal brain targeting is the trigeminal nerve pathway. The trigeminal nerve-an important cranial nerve V-innervates both the respiratory and olfactory regions of the nasal cavity, especially via its ophthalmic and maxillary branches. Such a route of absorption enables drugs to reach the pons and medulla and thus deliver to deeper brain structures that cannot be accessed only by the olfactory route of drug administration. Drugs administered intranasally are distributed widely throughout the brain, on both cortical and subcortical regions. Experimental studies have, in fact, validated the importance of this pathway. For example a study showed that intranasally administered fluorescently labeled nanoparticles appeared in the brainstem and cerebellum in as little as 30 minutes, supporting their trigeminal-mediated transport. This complementary mechanism provides a more homogeneous distribution of drugs across multiple brain regions-a critical advantage for disorders such as AD that affect both cortical and subcortical areas[27].

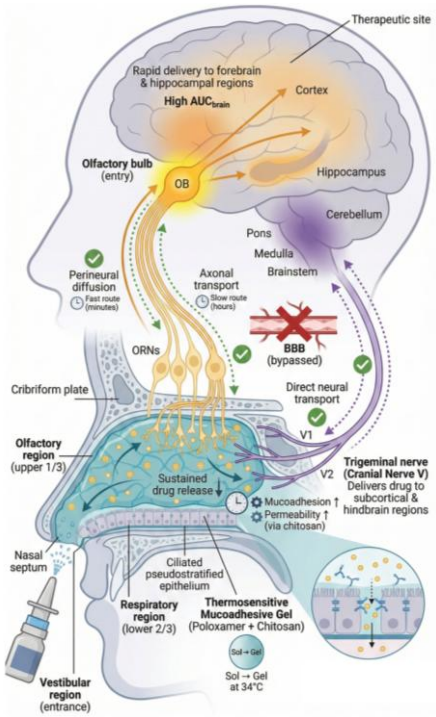

Figure 3 Challenges of Conventional Systemic Drug Delivery and the Advantages of Intranasal In-Situ Gels in Overcoming the Blood–Brain Barrier.

4.4 Pharmacokinetic Advantages of Nose-to-Brain Delivery:

In the intranasal route of drug delivery, the pharmacokinetic profile presents some advantages over the conventional systemic routes. The rapid onset of action arises from the direct transport pathways that bypass systemic circulation. This allows therapeutic agents to reach the brain within minutes-a significant advantage for managing neurodegenerative and acute neurological disorders. Furthermore, first-pass hepatic metabolism is completely avoided, with the effect of enhancing the bioavailability of drugs characterized by poor oral absorption or high metabolic degradation rates. Another key advantage associated with intranasal administration includes reduced systemic exposure. The drug acts mainly at the CNS levels, and thus there are very minimal chances of developing peripheral side effects, particularly in elderly patients suffering from AD, on polypharmacy regimens. Mucoadhesive formulations, such as in situ gels, increase nasal residence time due to their resistance against mucociliary clearance, thus ensuring sustained release of drugs and consistent plasma–brain concentration profiles[28].

Pharmacokinetic studies have also shown that the intranasal route results in higher brain-to-plasma ratios compared to oral or intravenous administration. For instance, reported that rivastigmine-loaded thermosensitive gels administered intranasally resulted in a 4.2-fold improved brain AUC compared to oral administration. Similar enhancements were noted with donepezil and curcumin formulations, thereby indicating that nasal delivery considerably improves targeting efficiency to the brains along with maintaining low systemic levels[29].

Another important advantage is the possible delivery of biopharmaceuticals and nanocarriers, including peptides, siRNA, and nanoparticles, which in their native form are unable to permeate the BBB. Formulation of such agents in mucoadhesive gels or as lipid-based carriers enhances their stability and allows for controlled diffusion across the nasal epithelium and neural channels. Together, these various pharmacokinetic advantages point to the intranasal pathway as an ideal means of drug delivery to the CNS. Factors that Affect Nasal Absorption of Drugs Despite this, however, intranasal delivery is affected by several physiological and formulation factors. The viscosity of nasal mucus, the rate of mucociliary clearance (generally every 15-20 minutes), the enzymatic degradation, and the molecular weight of the drug all have a crucial effect on absorption efficiency. Formulation attributes like pH, tonicity,

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particle size, and polymer composition also determine the extent of mucosal permeation and retention. Such limitations may be offset by the use of bioadhesive and penetration-enhancing excipients to ensure optimal uptake of the drug. Moreover, disease conditions, such as rhinitis or age-related mucosal atrophy, can alter nasal physiology, hence affecting drug deposition patterns. The development of robust, patient-tailored formulations is thus essential for consistent clinical outcomes[30].

5. In-situ Gel Drug Delivery Systems: Principles and Mechanisms:

In-situ gel systems for drug delivery represent an advanced and smart class of polymer delivery systems and are capable of exhibiting sol-gel transitions after administration. With these systems, it is possible to have a liquid/sol phase in an in-situ gel delivery system prior to administration, hence facilitating ease of administration. However, when they come into contact with a particular stimulus in physiological environments such as temperature, pH, or a certain level of ions, they transform to a gel state. The main advantages of using in-situ gel delivery systems include increased dwell time in the region of application, controlled delivery of drugs, increased bioavailability, and less frequent dosing[31].

The basic idea of in-situ gelation is based on a phase transition in a polymer solution because of a change in the surrounding environment, resulting in a partial solid formation that can entrap drugs. The phase transition is based on the polymer structure and interaction with the surroundings. As soon as gelation takes place, a three-dimensional network gets formed in which the diffusion of drugs gets hindered; hence, a sustained release system is formed. Based on modifications in polymer structure, in-situ gelation can be controlled[32].

On the basis of the nature of the external stimulus involved in gelation, in situ gelling systems can be classified into mainly two categories: pH-sensitive systems, ion-sensitive systems, and thermal-sensitive systems. Among them, thermal-sensitive systems have gained immense attention in recent years. They exist in a liquid state at room temperature but change into semisolid systems when heated above physiological temperatures. The cross-linking of polymers in thermal-sensitive systems relies on dehydration of polymer chains and subsequent formation of aggregates of micelles above the lower critical solution temperature (LCST) threshold. The most widely used biodegradable polymer in thermal-sensitive systems is Poloxamers, which is otherwise known by the trade name 'Pluronics.' They are a class of triblock polymers with a combination of both polyoxyethylene and polyoxypropylene in their structures. They are formed in a way to create a network of micelles that pack tightly when heated to physiological temperatures, leading to semisolid gel formation. They have gained immense attention in recent years in designing ophthalmic and nasal delivery systems because of their fast sol/gel transition time at physiological temperatures, resulting in increased residence times in nasal and ophthalmic sites with a subsequent boost in bioavailability. Chitosan and β-Glycerophosphate systems show thermal-sensitive gelation and have gained attention in designing ophthalmic and nasal delivery systems[33]. pH-sensitive gels function based on sol–gel transitions produced by variations in environmental pH. The sol–gel transition is based on the ionization of carboxylic or basic funcional groups in the polymer backbone, which affects polymer solubility and gel formation. Chitosan, a biodegradable polycationic polymer, is soluble in an acidic environment but undergoes gel formation when pH approaches neutrality. On the other hand, anionic polymers such as Carbopol and polyacrylic acid undergo gel formation at higher pH regions because of the ionization of carboxylic acid funcional groups. The pH-sensitive gel is an ideal drug delivery system for mucosal routes such as ophthalmic, vaginal, and oral delivery because it can function in a wide variety of pH environments. Moreover, when anionic polymers such as Carbopol coexist with chitosan in a physiological pH environment in regions such as the nasal mucosa or the intestines, fluids can gel, making them more suitable for sustained mucosal delivery due to increased adhesion[34].

Ion-sensitive gels represent another important type, which requires mono- and divalent ions for triggering gel formation. They usually employ carbohydrates such as gellan gum, alginate, and pectin. The gelation mechanism in such systems involves ion cross-linking between carboxylic ions in the polymer and ions such as calcium and sodium. Ion-sensitive gelation systems include gels of gellan, a bacterium called Sphingomonas elodea, which can form elastic gels in physiological concentrations of ions and have shown efficacy in ocular and nasal delivery systems. Sodium alginate gels work on an 'egg box model,' where guluronic acid cross-links in the presence of calcium ions. Such ion-sensitive systems are very effective in ocular delivery systems because they form an instant gel in tears containing ions when instilled in the eyes, resulting in an increased precorneal residence time with better efficacy[35].

Among these in-situ gel-forming polymers, chitosan, gellan gum, and poloxamers have a

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prominent role. Chitosan polymers are biodegradable, nontoxic, and have good mucoadhesive properties. Additionally, their cationic nature leads to better interaction with negatively charged mucous membranes, increasing mucoadhesion and permeability of drugs. When mixed with β-Glycerophosphate, it shows thermal responsiveness and readily forms a gel at physiological temperatures without altering its biocompatibility. Gellan gums are naturally derived anionic polysaccharides, which form ion-sensitive gels in response to cations present in nasal fluid, tears, and gastrointestinal fluid. They have a high degree of elasticity and transparence and are widely used in ophthalmic and nasal delivery systems. Poloxamers, being synthetic amphiphilic polymers, show reversible thermal gelation and are usually mixed with other mucoadhesive polymers for optimized fluidity, mucoadherence, and thermal gelation depending upon the desired route of delivery[36].

The gelation mechanisms in these systems vary depending on the stimulus but basically involve a common principle of a phase transition. In thermo-responsive systems, the rearrangement of micelles and hydrophobic interaction contributes to a dense gel network with increasing temperatures. In pH-sensitive systems, ionization promotes a balance between hydrophilic and hydrophobic forces, leading to a reduction in solubility and subsequent cross-linking. Ionic activation systems make use of cross-linking via cations to create a gel-like structure from a polymer liquid solution. Some systems involve a combination of two or more stimuli, such as temperature and ionic responsiveness. The performance of a formulation is influenced by a variety of important parameters. The concentration of the polymer is a very important factor because it determines the viscosity, strength, and gelation temperature of a gel. The critical concentration ensures a better injectability or ease of administration with a better gel network formation at a desired site of application. The environmental parameters such as pH, ionic strength, and temperature influence gelation rate and need to be optimized depending upon the desired site of application. Mutual interaction of the drugs with polymers affects gelation properties and release rate of drugs. Hydrogen bonding or electrostatic interaction can be used to stabilize a system or control a release rate, depending upon a particular formulation. Additives such as surfactants, copolymers, and/or viscosity regulators are incorporated into a formulation to control rheology and gelation properties. In situ gels have a multitude of therapeutic benefits. The capability of in situ gels to gel in response to interaction with the physiological environment is responsible for localized delivery and controlled release of drugs. Additionally, in situ gels are in a liquid state before administration, making them simple to deliver using syringes or dropping systems, thus improving patient compliance. Furthermore, their application using biodegradable and biocompatible polymers is non-toxic. Moreover, the possibility of varying polymer composition gives room for developing a variety of drugs, including small molecule drugs, peptides, and nanoparticles. However, a few issues remain in the development and application of in-situ gels. Incompatibility of polymers with drugs can be an issue in terms of shelf stability and release behavior. Variations in physiological parameters such as mucus composition in noses or electrolyte concentrations in tears can impair gel reproducibility. Some in-situ gels can suffer from burst release issues because of lower cross-linking and poor gelation properties. In addition, storage and sterilization procedures can impact polymer structure, which affects gelation behavior. Briefly stated, in situ gel drug delivery systems have a profound and highly versatile role in controlled and targeted drug delivery. They make use of physiological stimuli such as temperature, pH, and ion concentration, which bring about a liquid to gel transition, thereby ensuring sustained release. Examples of such systems include poloxamer-based thermoresponsive systems, pH-sensitive chitosan-derived gels, and ion-activated gellan gum matrices. Further research in polymer chemistry and nanotechnology can potentially address existing shortcomings and bring in situ gel systems into broader therapeutic application in order to achieve a significant milestone in intelligent, patient-centric, and efficient drug delivery systems.[37]

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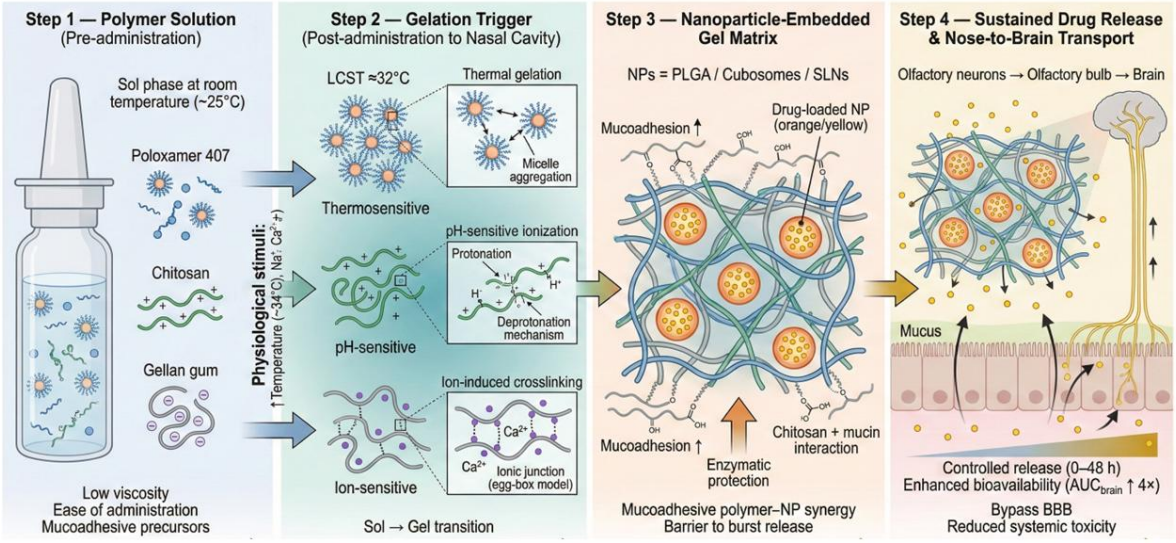

Figure 4 Mechanism of Sol–Gel Transition and Nanoparticle Integration in Intranasal In-Situ Gel Systems for Controlled Nose-to-Brain Drug Delivery.

Table 1. Classification of In-situ Gelling Mechanisms and Representative Polymers

Stimulus Type	Mechanistic Trigger	Representative Polymers	Advantages	Limitations / Optimization Needs
Thermosensitive Gels	Sol–gel transition triggered by temperature (30–35°C)	Poloxamer 407, Poloxamer 188, Pluronic F-127	Rapid gelation after nasal administration, patient comfort, reproducible transition	Temperature sensitivity affected by polymer concentration and nasal cooling effect
pH-sensitive Gels	Polymer ionization at nasal pH (≈6.5)	Carbopol 934, Polyacrylic acid, Eudragit E100	Protects labile drugs, adjustable gelation	Sensitive to nasal pH variation and buffer capacity
Ion-activated Gels	Gelation triggered by cations (Na^+, Ca^{2+} in nasal mucus)	Gellan gum, Sodium alginate, Pectin	Immediate gel formation upon contact with nasal fluid, prolonged retention	Ion concentration variability may affect consistency
Mucoadhesive Hybrid Gels	Physical and electrostatic adhesion to mucin glycoproteins	Chitosan, HPMC, Hyaluronic acid	Prolonged residence time, enhanced absorption	Excess viscosity may hinder ciliary function
Stimuli-responsive / Hybrid Systems	Multiple triggers (temp + pH or ion) integrated	Poloxamer–Carbopol, Poloxamer–Gellan hybrids	Tailored control over gelation and release kinetics	Complex optimization required for stability and reproducibility

6 Intranasal In-situ Gels for Alzheimer's Therapy: Current Evidence:

The intranasal route has gained enormous attention within the past decade as a promising alternative pathway for central nervous system drug delivery. The capabilities of this route to bypass the BBB through olfactory and trigeminal neural pathways allow the direct transport of drugs into the brain with reduced systemic exposure and increased therapeutic efficacy. In the case of AD, where conventional therapies are plagued by low CNS bioavailability and peripheral toxicity, intranasal in-situ gels have emerged as an innovative solution that combines mucoadhesion, sustained release, and non-invasive delivery. Encouraging outcomes with diverse polymeric and nanocomposite in-situ gels, specifically those incorporating cholinesterase inhibitors, antioxidant phytoconstituents, and neuroprotective agents, have recently been demonstrated in various preclinical and emerging clinical studies[38].

6.1 Preclinical Studies: Advances in Formulation Design and Efficacy:

Most of the preclinical studies have focused on the optimization of in situ gel formulation composition for efficient brain targeting. Various studies conducted from 2023 to 2025 emphasize the potential of thermo-, ion-, and pH-sensitive gels based on different polymers like poloxamer 407, chitosan, gellan gum, and carbopol. For example, a study in 2025 developed a lutein-loaded intranasal thermosensitive in-situ gel composed of poloxamer 407, poloxamer 188, and hydroxypropyl methylcellulose. The developed formulation showed fast transition of sol to gel at nasal

physiological temperature 33-35°C and significantly enhanced brain bioavailability, showing three-fold increase in lutein concentration within hippocampus and cortex in comparison with oral suspension. Further, Morris water maze behavioral analysis indicated improved spatial memory and cognitive recovery in β-amyloid-induced AD rats, showing pharmacodynamic efficacy and neuroprotection. Similarly, developed an in situ gel system incorporating donepezil-loaded BSA nanoparticles. The hybrid system demonstrated mucoadhesive strength that was superior and provided sustained release over a period of 24 hours with more than 80% of the drug retained in the nasal mucosa. The pharmacokinetic profile revealed that the brain bioavailability increased by 4.5 times over that observed with oral donepezil hydrochloride. Immunohistochemistry further confirmed that amyloid plaque formation was significantly attenuated with restoration of cholinergic neuron density in the hippocampus region. The study concluded that incorporation of nanoparticles into an in-situ gel besides offering protection against enzymatic degradation ensures better residence and transport across olfactory epithelia[39].

A parallel study developed CNS & Neurological Disorders - Drug Targets, 2025, investigated rivastigmine-loaded mucoadhesive nanoparticles incorporated into an ion-activated gellan gum gel. The system was optimized for gelation at ionic strengths comparable with those of nasal fluids, forming a stable matrix within seconds. Pharmacodynamic evaluations showed enhanced learning indices and reduced acetylcholinesterase activity in scopolamine-induced amnesic rats. Histopathological investigations demonstrated marked neuronal preservation and reduced oxidative stress markers, confirming neuroprotection through enhanced brain targeting. Other recognizable preclinical works have studied the delivery of natural neuroprotectants and antioxidants. Similarly as study in 2025 developed a pH-sensitive chitosan–carbopol gel containing curcumin with excellent mucoadhesion and maintaining a release profile up to 10 hours. Intranasal administration of intraperitoneal injection yielded a brain curcumin concentration almost fourfold higher than that from intraperitoneal injection. Histopathological, biochemical, and behavioral studies demonstrated significant reductions in reactive oxygen species (ROS) and lipid peroxidation, indicating enhancement of the antioxidant defense. In a similar pattern, Singh et al. (2024, Drug Delivery Letters) reported on the development of quercetin-loaded poloxamer–chitosan gels that reversed memory deficits and inhibited tau hyperphosphorylation in AD rats, thus illustrating the role of phytochemicals delivered via intranasal gels in mitigating AD pathology[40].

6.2 In situ Gels with Nanotechnology Integration

The recent approaches involve the incorporation of nanocarrier systems (such as liposomes, nanoparticles, cubosomes, and solid lipid nanoparticles) into in-situ gel matrices for enhanced stability and bioavailability. This dual system combines the advantages of both nanoparticles and gels with regard to controlled release while maintaining mucosal adhesion and avoiding rapid mucociliary clearance. For example, A study designed a multifunctional cubosome-integrated thermoresponsive gel for the co-delivery of memantine and galantamine. The system showed an encapsulation efficiency for a dual drug above 85%, with sustained release for 36 hours. In Wistar rat brain pharmacokinetics, the brain-to-plasma ratio increased fivefold, while biochemical assays indicated enhanced cholinergic neurotransmission and neuroinflammation attenuation. Fluorescence imaging demonstrated the presence of cubosomes in olfactory bulbs and cortical regions within 30 min following administration, which reflected the efficacy of the nose-to-brain route. The same principle was utilized another study in 2025, where they developed a thermoresponsive *in-situ* gel containing dispersed poly(lactic-co-glycolic acid) nanoparticles loaded with rivastigmine in a poloxamer 407 matrix. The hybrid system thus obtained demonstrated a controlled release profile for 48 hours, reduced plasma peaks of the drug, and thereby superior cognition performance in Morris water maze and Y-maze tasks. Neuronal survival, along with decreased oxidative stress in the hippocampus, was also reported, which established the superiority of nanoparticle-loaded gels over conventional systems[41].

7. Pharmacodynamics & Mechanistic Insights:

Pharmacodynamic outcomes arising from intranasal in-situ gels have consistently exhibited improved cognitive function, reduced amyloid pathology, and neuroprotection. In this regard, rapid onset of action, higher brain accumulation, and longer retention of drugs delivered intranasally have been reported in various studies as compared to oral or intravenous routes of administration. Mechanistically, this improvement arises due to three synergistic effects: mucoadhesion, controlled release, and direct neural transport. The mucoadhesive polymers-chitosan, gellan gum, and carbopol-interact with the negatively charged sialic acid residues in the nasal mucosa, enabling prolonged residence time and intimate contact for absorption. The controlled release property imparted by thermosensitive or ion-activated gels

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maintains the sustained diffusion of drugs through the olfactory neurons. Besides, this direct neural transport bypasses the BBB, hence facilitating drug delivery to key regions such as the hippocampus, amygdala, and cortex, which are considered the principal sites of AD pathology. Preclinical molecular studies further illustrate that drugs delivered through intranasal gels could influence multiple signaling cascades of importance in AD. Donepezil and rivastigmine gels increased acetylcholine levels and inhibited cholinesterase activity, whereas curcumin and quercetin formulations decreased amyloid-β aggregation, oxidative stress, and tau phosphorylation. In some hybrid preparations, the addition of antioxidant excipients or metal chelators has exhibited synergistic effects by diminishing neuroinflammatory pathways mediated through NF-κB and TNF-α[42].

7.1 Mechanistic Perspectives on Enhancing Brain Bioavailability:

The brain is considered to be one of the most promising targets in pharmacology despite being a challenge because of the presence of the blood–brain barrier (BBB) in the brain, an intricate structure and function interface that safeguards the central nervous system from any noxious substance in addition to restricting anabolic drugs. To bypass this challenge with relative ease in a non-invasive manner and without increasing latency in treatment, intranasal in-situ gel formulations have emerged with a high degree of promise based on the unique characteristics presented by the intranasal route targeting the brain with a direct pathway via olfactory and trigeminal nerves. Their mucoadhesive qualities, slow release capabilities, and prospects of efflux transporter modulation using P-gp make way for a greatly enhanced brain availability of drugs[44].

7.2 Sustained Release & Controlled Kinetics:

Sustained release is another important characteristic of in situ gels which enhances brain bioavailability by ensuring an ideal constant release of drugs into the CNS. Thus, after gel formation, a polymer network serves as a diffusion barrier with a controlled release of the drug encapsulated in the polymer into the nasal mucosa. The rate of release is influenced by variables such as polymer composition, cross-linking density, and environmental factors such as temperature and pH[44].

Table 2. Safety, Regulatory, and Translational Evaluation Parameters for Intranasal In-situ Gels

Evaluation Category	Test / Assessment	Purpose	Guideline / Reference Standard	Key Translational Considerations
Mucosal Safety	Histopathology, Scanning Electron Microscopy, Mucociliary Clearance Test	Detect epithelial damage and ciliary dysfunction	FDA & EMA Nasal Product Guidance (2023 update)	Long-term exposure studies (≥90 days) recommended for chronic neurotherapies
Physicochemical Stability	Rheology, Gelation Temperature, Drug Retention	Ensure reproducible gel formation and storage stability	ICH Q1A(R2) Stability Testing	Must maintain gelling ability at 30–40°C during shelf life
Pharmacokinetic Modeling	Plasma and Brain AUC, Tmax, Cmax	Quantify nose-to-brain targeting and systemic exposure	OECD 417 Pharmacokinetics Guideline	Digital twin modeling to predict human brain deposition
Device Performance	Spray pattern, Droplet size, Dose uniformity	Confirm reliable intranasal deposition	USP <601> Aerosols and Nasal Sprays	Compatibility of gel viscosity with metered-dose devices required
Regulatory Approval Pathway	NDA (US FDA), MAA (EMA)	Define combination product classification	FDA/CDER/CDRH Joint Review Protocols	Combination of drug + delivery device mandates dual compliance
Clinical Translation	Phase I safety, Phase II cognitive efficacy, Phase III comparison with oral therapy	Validate human safety and cognitive outcomes	ICH E6(R3) Clinical Practice Guidelines	Nasal endoscopy and olfactory testing integral to clinical evaluation

8. Crossing the Blood-Brain Barrier:

The most important benefit derived from intranasal in-situ gels is their capacity to completely bypass the BBB, which targets the brain via direct neural routes. Olfactory pathways, present in the upper part of the nasal passages, establish a direct route from the nasal mucosa to the olfactory bulb via olfactory sensory neurons. Other pathways include the trigeminal pathway, which targets the brainstem and spinal cord in addition to connecting with the nasal mucosa. Such drugs can reach their targets via intracellular transport using axonal transport systems or via perineuronal pathways, thus bypassing the tight lining of the BBB. Intranasal in-situ gels improve this route by ensuring sustained local residence of the drug in these upper regions for efficient uptake. Their viscoelastic properties can effectively prevent runoff of higher amounts of drugs into the gastrointestinal tract and allow better interaction with olfactory/trigeminal epithelia. A 2024 study showed that intranasal in-situ gel formulations of rivastigmine demonstrated "efficiency of brain targeting of more than 60%, where targeting of the drug in hippocampus and

cortex regions of the brain has been demonstrated with fluorescence imaging after 30 minutes of intranasal dosing. [45]

8.1 Novel Strategies and Emerging Formulations:

From conventional polymeric gels, the latest surge in research on intranasal in-situ gel systems for brain targeting has been focused on highly engineered multifunctional systems integrating nanotechnology, stimuli responsiveness, and biomolecular delivery platforms. Such innovations are targeted at surmounting persistent challenges in central nervous system (CNS) therapeutics, which relate to poor drug solubility, rapid mucociliary clearance, and complex blood–brain barrier (BBB) permeability. Advanced nanoparticle-loaded gel formulations down to hybrid stimuli-responsive systems are currently being developed to efficiently deliver small molecules, peptides, and genetic materials to the brain with transformative potential for neurodegenerative diseases such as Alzheimer's disease (AD)[46].

8.2 In-Situ Gels-Loaded Nanoparticles:

NP-loaded in-situ gels are a synergistic strategy, combining the controlled release and mucoadhesive properties of hydrogels with the nanocarrier's enhanced transport capabilities. Such systems enable dual-level control: nanoparticles protect and provide sustained release of the drug, while the gel matrix maintains the residence time at the nasal mucosa, promoting direct nose-to-brain transport. An 2025 study illustrated the efficiency of a donepezil-loaded bovine serum albumin nanoparticle embedded in a thermosensitive poloxamer-HPMC gel. This system could achieve extended drug release over 24 hours and enhanced brain targeting efficiency 4.5 times that of oral donepezil. Pharmacodynamic analysis showed remarkable cognitive recovery and amyloid burden diminution in transgenic AD mice[47].

8.3 Stimuli-Responsive In-Situ Gels:

Stimuli-responsive gels, or "smart" gels, are a new generation of adaptive delivery systems that could respond against modifications of the environment depending on temperature, pH, ionic concentration, or enzymatic activity, among other changes. These gels show dynamic physicochemical transformations that control gelation, drug release, or degradation in order to provide ondemand and site-specific drug delivery[48].

8.4 In-Situ Gels for Peptide and Gene Delivery:

The most significant challenge for delivering peptides, proteins, and nucleic acids to the CNS has been enzymatic degradation and impermeability across the BBB. Intranasal in-situ gels can provide protection by encapsulation along with direct transport via neurons. In situ gels incorporating hybrid formulations of cationic nanoparticles, such as polyethyleneimine or chitosan nanoparticles, for carrying siRNA or plasmid DNA, have been developed. Developed an in situ-gelling formulation of a chitosan-gellan gum-based system incorporating BACE1-targeting siRNA-loaded lipid nanoparticles. The BACE1 gene targets a key enzyme in amyloid-β production. The formulation showed >70% gene silencing efficiency in neuronal cultures and significant amyloid reduction in vivo. Besides that, peptide-based nanogels are being studied for dual functionality, acting as both drug carriers and therapeutic agents. Li et al., 2025, Nano Today, for the very first time presented a self-assembling peptide hydrogel with incorporated neurotrophic factors inducing neuronal regeneration. Locally administrated by the nasal route, this gel supported sustained local release of growth factors, thus enhancing synaptic plasticity and memory performance in the AD models[49].

8.5 Hybrid systems with multiple functions:

Recent trends are focused on the design of hybrid multifunctional systems that combine several stimuli-responsiveness, nanocarriers, and therapeutic modalities into a single platform. These are complex systems that would integrate diagnostic, therapeutic, and protective functionalities, representing one step toward theranostic nanogels. Das et al. 2025, Journal of Drug Delivery Science and Technology, therefore, illustrated a temperature- and ionic stimulus-responsive cubosomal gel for the dual-drug approach that allowed the synchronized release of hydrophilic and hydrophobic drugs. The hybrid formulation also contained antioxidant excipients, reaching triple-action neuroprotection, cholinergic enhancement, and modulation of oxidative stress[50].

9. Challenges, Safety, and Regulatory Considerations:

Intranasal in-situ gel drug delivery systems have emerged as a promising frontier in targeting neurodegenerative disorders, especially Alzheimer's disease. However, despite the significant advances made in formulation science and preclinical outcomes, several challenges hinder their clinical translation. These include physiologic barriers of mucociliary clearance, chronic nasal toxicity, poor patient compliance, and regulatory complexities in the evaluation of long-term safety and efficacy. Identification of these aspects is crucial to translate from laboratory innovation to therapeutic reality[51].

9.1 Mucociliary Clearance and Nasal Physiological Barriers:

The nasal cavity is lined with mucociliary epithelium, responsible for the entrapment and

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clearance of foreign particles through a coordinated movement of cilia and mucus flow. While this has an important role in respiratory defense, it provides a big barrier to drug delivery. The residence time of the formulation within the nasal cavity is normally below 20 min, which leads to a fast clearing of the drug-loaded gels or solutions before a considerable amount of absorption can take place. In-situ gels have been specifically engineered to avoid this shortcoming by mucoadhesive polymers, including chitosan, gellan gum, carbopol, and hydroxypropyl methylcellulose (HPMC). Gelation kinetics also changes with the change in temperature and pH fluctuations. As an example, extremely fast gelation blocks the airflow or causes discomfort, whereas too slow gelling systems result in quick loss due to its drainage. To meet such challenges, the thermoresponsive systems were optimized in which poloxamer concentration allowed Varshney and Singh to develop an in situ gel within 2 minutes at 34°C by maintaining spreadability and mechanical integrity. Therefore, rheological tuning remains a good strategy for overcoming mucociliary clearance without compromising comfort[52].

9.2 Long-Term Nasal Toxicity and Histopathological Considerations:

Chronic administration of intranasal formulations is especially concerning in the case of diseases like Alzheimer's that require long-term therapy. In such cases, the major concerns are local toxicity and mucosal changes. The epithelial architecture of the nasal mucosa is very fragile and susceptible to chronic exposure to surfactants, preservatives, and high concentration of polymers. Chronic irritation can lead to inflammation, epithelial erosion, and damage to the cilia; this might affect olfactory function or cause anosmia. A 2024 study reported the long-term nasal administration of thermosensitive in-situ gels for six months in rats and found that high dosing frequencies exerted mucosal thickening with an increase in the goblet cell count. These observations emphasize the requirements of a long-term study on biocompatibility, especially in formulations using cationic polymers such as chitosan, that could interrupt tight junctions, leading to alteration in epithelial permeability[53].

9.3 Patient Compliance and Practical Considerations:

Patient compliance is an important determinant of therapeutic success. Intranasal administration is typically noninvasive and more acceptable than injections; however, the acceptability of in-situ gels relies on their sensory attributes, such as texture, viscosity, and feeling upon administration. Gels with excessive viscosity or poor spreadability tend to provoke nasal blockage or discomfort. Formulations must therefore be designed to remain liquid during administration and transform into a gel within seconds after contact with the nasal mucosa. Smell or taste of formulations might also influence the patients to accept the therapy, especially in geriatric patients due to their increased sensitivity of olfaction or disturbed cognitive conditions. To improve acceptability, odorless and tasteless polymers are being used with minimal excipients. In design, the device also plays its role: multidose pump sprays, unit-dose applicators, metered nasal atomizers allow controlled dosing and also minimize contamination [54].

9.4 Barriers from a Regulatory and Translational Perspective:

Regulatory approval for intranasal in-situ gel formulations remains complex because of the hybrid nature of these systems, which combine features of liquid, semi-solid, and particulate drug delivery platforms. The FDA classifies nasal formulations under the category of combination products if they integrate a drug with a delivery device; thus, they are subjected to dual regulatory pathways under CDER and CDRH. Regulatory agencies insist on sufficient physicochemical characterization, which includes gelation temperature, rheological behavior, mucoadhesive strength, in-vitro release kinetics, and in-vivo correlation studies. Long-term stability testing according to the International Council for Harmonisation guideline should be compulsory in order to establish polymer integrity and retention of the drug. For nanoparticle-loaded gels, particle size distribution, zeta potential, and degradation kinetics should be followed over the storage period. Toxicological studies also need to address local irritation, the integrity of the olfactory bulb, and systemic exposure after chronic administration. The FDA recommends validated animal models, including rats and rabbits, for nasal histopathology, while non-human primate models are preferred for pharmacokinetic and safety extrapolation to humans[55].

10 Future Perspectives:

The future of intranasal in situ gel delivery systems for Alzheimer’s will be where innovative breakthroughs in materials science, personalized medicine, AI-assisted design formulations, and translation research coalesce. Although existing work has proved successful in achieving enhanced pharmacokinetics and neuroprotection effects in preclinical studies, a future-oriented approach would focus on bringing forth a combination of smart polymers, personalized therapies, and model predictions to enhance brain delivery[56].

Current breakthroughs in polymer research are upending the traditional idea of in-situ gel systems. Passive delivery systems are being replaced with 'dynamic systems responsive to external stimuli.' Current trends in this area include developing 'multi-stimuli-responsive gels in which gelation can be achieved in response to a combination of stimuli such as temperature, pH, and ion concentration.' For example, a dual-sensitive hydrogel containing poloxamer and carbopol derivative, which responded simultaneously to nasal pH and temperature, leading to enhanced residence time without mucosal irritation. Recently, next generation intranasal gel formulations are incorporating nanotechnology-based systems such as lipid-polymer hybrid nanoparticles, dendrimers, and cubosomal carriers into their design. "Varshney and Singh have shown that a five-fold higher brain concentration can be attained when donepezil-loaded polymeric nanoparticles were incorporated in a thermoresponsive gel compared to conventional intranasal delivery systems," according to a paper of 2025. Nano-hybrid systems targeting ADM with antioxidants and neuroprotective peptides have emerged with a focus on multifunctional therapy, thereby targeting amyloidosis, tau phosphorylation, and neuroinflammation simultaneously[57].

Additionally, biomimetic hydrogels which imitate the viscoelastic properties of nasal mucus are being developed with enhanced mucoadherence and biocompatibility. Materials such as hyaluronic acid, gelatin, and fibroin of silk have demonstrated efficacy in sustaining mucosal integrity with chronic delivery. The future course of this technology might include self-healing gel systems with dynamic nasal capabilities of restoring their structure despite mechanical disruption[58].

Personalized medicine is a revolutionary approach in the future of Alzheimer's treatment. With varying patient progression, genetic makeup, and physiological differences in patients with nasal passage physiology, individualized intranasal in-situ gel formulations can unlock a whole dimension in treatment optimization. Pharmacogenetic information can help in pharmaceutical usage and frequency, and imaging studies can assist in individualized delivery factor customization. In Alzheimer's, in which case early-stage diagnosis and progression rate can be highly variable, AI-driven predictive algorithms might have linked patient markers such as cerebrospinal fluid amyloid, APOE4 alleles, and imaging studies to optimal drug release profiles. Such a personalized strategy might have ensured a relevant level of neuroprotective or disease-modifying drugs in intranasal formulations. Customized dosing delivery devices represent another such area. Future nasal delivery devices could have biosensors capable of assessing hydration levels, temperature, and airflow before adjusting spray volume and activating gelation. Such an adaptive dosing system would potentially allow a consistent level of delivery regardless of physiological differences among patients[59].

Artificial intelligence and machine learning functions are expected to have critical roles in the rational design, optimization, and translation of intranasal in-situ gels. AI algorithms can analyze an enormous amount of information including polymer chemistry, rheology, drug solubility studies, and in vivo pharmacokinetics to arrive at optimized formulations with a minimal number of experimental cycles. To illustrate, an AI-assisted model in 2025 predicted sol-gel transition temperatures, viscosities, and mucoadhesive strengths of thermosensitive gels using polymer composition and molecular weight. Predictive capabilities will enable scientists to shortlist possible formulations without synthesizing them in a lab, resulting in immense savings in time and money. In a similar manner, ML models can investigate relationships between polymer microstructure and release rates, making way for predictions concerning in vivo performance[60].

Furthermore, AI systems can model nose-to-brain pharmacokinetics, which combines models of the nasal passages with mathematical equations of diffusion. AI can forecast the path a drug molecule takes from nasal mucosa to brain and work on developing formulations overcoming barriers to this pathway. Artificial intelligence-powered image analysis and computer vision can potentially be used for automatic toxicity evaluation based on histopathology slide analysis for mucosal changes, thus fast-tracking safety evaluation. At a translational level, regulatory science tools are anticipated to incorporate AI-powered predictive toxicology systems for safety evaluation and mucosal compatibility assessment of excipients[61].

The translation of preclinical successes into a clinical setting is an important priority in this area. Successful translation is largely dependent on a rigorous validation of safety, efficacy, and reproducibility. High-quality in-vitro models such as 3D human nasal mucosa culture systems and microfluidic 'nose-on-a-chip' devices are predicted to replace animal models in order to forecast human mucosal responses in a conventional manner. They allow real-time analysis of gel-mucosa interaction, absorption, and neuronal transport. Furthermore, a solution to scalability in clinical-grade manufacturing is a topic that must be

considered. The technology of continuous manufacturing and 3D printing may potentially facilitate the production of patient-specific gels with controlled microarchitecture and polymer composition under an on-demand approach. The FDA and EMA are expected to have new guidelines when dealing with hybrid systems incorporating nanotechnology and in-situ gelling systems.[62]

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