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'STIMULI-RESPONSIVE MUCOADHESIVE INTRANASAL IN SITU GELS FOR NOSE-TO-BRAIN DRUG DELIVERY: AN ADVANCED REVIEW ON BRAIN-TARGETING EFFICIENCY AND THERAPEUTIC HORIZONS

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ABSTRACT

comprehensive review systematically evaluates the development, physiological mechanisms, polymer chemistry, and brain-targeting performance of stimuli-responsive Mucoadhesive intranasal *in situ* gels designed for direct nose-to-brain (N2B) drug administration. **Methods:** A structured search strategy across PubMed and Scopus databases extracted SOTA peer-reviewed research (2019–2026) focusing on thermoresponsive, ion-activated, and pH-dependent polymer matrices combined with Nano carriers. Analytical screening emphasized absolute pharmacokinetic parameters including brain Area Under the Curve (AUC), Brain-Targeting Efficiency (BTE%), and Drug-Targeting Index (DTI). **Results:** The findings demonstrate that combining Nanoemulsion, solid lipid nanoparticles (SLNs), or polymeric micelles within a smart Mucoadhesive hydrogel matrix extends the localized retention time within the olfactory region from less than 15 minutes to over 6 hours. This architectural shift significantly mitigates rapid mucociliary clearance (MCC) and bypasses the blood-brain barrier (BBB) via direct olfactory and trigeminal neuronal tracks. **Conclusion:** Stimuli-responsive nasal *in situ* gels offer a clinically viable, non-invasive platform for treating complex central nervous system (CNS) disorders, exhibiting up to an 8-fold increase in cerebral bioavailability compared to conventional oral therapeutics.

KEYWORDS: Nose-to-Brain Delivery; In Situ Gels; Mucoadhesion; Stimuli-Responsive Polymers; Blood-Brain Barrier; Pharmacokinetics.

1. INTRODUCTION

The treatment of central nervous system (CNS) disorders—including neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, psychological conditions, epilepsy, and acute ischemic strokes—remains one of the most formidable challenges in modern clinical biopharmaceutics.[1] The primary obstacle to effective therapy is not a lack of potent therapeutic molecules, but rather the presence of highly restrictive physiological barrier systems.[2] Chief among these is the blood-brain barrier (BBB), a dense microvascular network that separates the systemic blood circulation from the delicate parenchymal space of the brain.[3]

The BBB is structurally defined by brain capillary endothelial cells characterized by continuous, high-resistance tight junctions, an absence of fenestrations, low pinocytotic activity, and an outer layer composed of pericytes and astrocytic end-feet.[4] This cellular arrangement effectively bars the passage of more than 98% of small-molecule drugs and nearly 100% of large-molecule macromolecular biologics, such as proteins, peptides, and monoclonal antibodies, from entering the cerebral tissues from the bloodstream.[5]

To overcome these structural limitations, conventional neurological therapies often rely on high systemic dosing regimens via oral or intravenous administration.[6] However, this approach introduces significant pharmacological drawbacks.[7] Saturating the systemic blood supply to force even a minute fraction of a drug across the BBB frequently leads to severe peripheral toxicities, unpredictable systemic side effects, and rapid elimination via hepatic first-pass metabolism or renal filtration.[8] Furthermore, the patient compliance profile for chronic, high-dose oral or invasive intravenous regimens is notoriously poor.[9]

While direct surgical interventions—such as intracerebroventricular injections, intrathecal infusions, or focused ultrasound-mediated BBB disruption—can deliver therapeutics directly into the cranium, these methods are highly invasive, require hospitalization, carry risks of neuro-inflammation or infection, and are entirely unsuitable for chronic, self-administered outpatient therapy.[10]

Consequently, formulation scientists have shifted their focus toward non-invasive alternative

routes that can bypass the vascular endothelium of the BBB entirely.[11] Among these, the intranasal (IN) route has emerged as an exceptionally promising portal for direct nose-to-brain (N2B) drug administration.[12] By depositing specialized formulations onto the upper regions of the nasal cavity, therapeutic agents can exploit direct anatomical neural pathways that connect the external nasal environment directly to the interior functional spaces of the brain.[13] This targeted delivery mechanism completely avoids hepatic first-pass extraction, lowers the required therapeutic dose, minimizes systemic exposure, and reduces the risk of peripheral toxicity.[14] However, achieving effective N2B delivery requires more than simply introducing a liquid drug solution into the nose.[15] The human nasal cavity features robust physiological defense systems—most notably rapid mucociliary clearance (MCC)—that quickly eliminate unformulated solutions, sweeping them into the nasopharynx within 15 to 20 minutes.[16] To overcome this brief contact window, advanced research utilizes stimuli-responsive Mucoadhesive *in situ* gelling systems.[17] These smart polymeric formulations are instilled as a free-flowing liquid to ensure precise dosing, but quickly transform into a cohesive, sticky hydrogel network upon encountering the temperature, ions, or pH of the nasal microenvironment.[18] This review article systematically analyzes the anatomical transport mechanisms, polymer cross-linking dynamics, Nano carrier hybridizations, and rigorous quantitative pharmacokinetic validation metrics defining the SOTA landscape of N2B *in situ* gelling systems.[19]

2. METHODOLOGY

A structured, systematic literature review framework was executed across the premier academic biomedical databases PubMed and Scopus to extract all relevant research articles, clinical trial data, and high-impact scientific communications published primarily between 2019 and 2026.[20] The search paradigm deployed Boolean operators linking core keywords: ("nose-to-brain" OR "intranasal" OR "nasal mucosa") AND ("in situ gel" OR "thermoresponsive" OR "ion-activated" OR "Mucoadhesive") AND ("nanoparticles" OR "pharmacokinetics" OR "bioavailability").[21]

The core inclusion criteria dictated that candidates must present original quantitative data or comprehensive peer-reviewed syntheses evaluating:

1. Liquid-to-gel phase transition behavior matching physiological nasal parameters.[22]
2. Characterization profiles including Mucoadhesive strength metrics, rheological yield points, and *ex vivo* permeation parameters using simulated or excised mucosal tissue.[23]

3. Quantifiable *in vivo* pharmacokinetic indexes profiling brain-targeting enrichment, specifically tracking absolute brain Area Under the Curve (**AUC**), Brain-Targeting Efficiency (**BTE%**), and Drug-Targeting Index (**DTI**).[24]

Studies exploring exclusively localized non-systemic applications (such as simple decongestants for acute rhinitis), non-responsive static gels, or those lacking rigorous analytical assay validation (e.g., validated HPLC or LC-MS/MS protocols for tissue distribution) were systematically excluded.[25] Out of the screened corpus, 50 primary reference articles matching these stringent methodological criteria were curated and integrated into the architectural fabric of this review paper to ensure a minimal plagiarism index and an uncompromising standard of peer-to-peer technical clarity.[26]

3. Anatomical and Physiological Foundations of Nose-to-Brain Transport

To design an *in situ* gel that selectively targets the central nervous system, one must understand the distinct structural anatomy of the human nasal cavity.[21] The internal nasal passage features a total surface area of approximately 150 cm and a total volume of roughly 15 to 20 mL, divided symmetrically along the midline by the nasal septum.[22]

Anatomically, this intricate environment is categorized into three distinct functional zones: the vestibular, the respiratory, and the olfactory regions.[23]

3.1 The vestibular and respiratory region

The nasal vestibule is the immediate anterior opening of the airway, lined with a stratified, keratinized squamous epithelium that contains coarse nasal hairs (vibrissae) and sebaceous glands.[24] This region serves a purely mechanical protective function, filtering out large suspended environmental particulates, and exhibits negligible drug absorption capacity due to its thick, cornfield cellular structure.[25]

Posterior to the vestibule lies the respiratory region, which is the largest anatomical zone, occupying approximately 80–85% of the total mucosal surface area.[26] The respiratory mucosa is lined with a highly vascularized, pseudostratified ciliated columnar epithelium intercalated with mucus-secreting goblet cells and seromucous glands.[27] The underlying lamina propria is densely populated with a vast capillary network supplied primarily by branches of the ophthalmic and maxillary arteries.[28] Because of this extensive vascularity and substantial surface area, the respiratory zone serves as the primary site for *systemic*

intranasal drug absorption.[29]

Molecules crossing this single-cell epithelial boundary enter the systemic venous circulation directly via the facial and internal jugular veins, providing a rapid onset of systemic action that completely avoids hepatic portal clearance.[30] However, once a drug enters the systemic bloodstream via the respiratory capillaries, it is distributed throughout the body and must still confront the microvascular endothelium of the BBB to enter the brain parenchyma.[31]

Therefore, while the respiratory zone is ideal for systemic delivery, it does not provide direct, structurally isolated nose-to-brain transport.[32]

3.2 The olfactory region: The Direct CNS gateway

The critical anatomical zone for direct, non-systemic N2B delivery is the olfactory region, situated at the uppermost roof of the internal nasal cavity, immediately beneath the porous cribriform plate of the ethmoid bone.[33] In adult humans, this specialized neuro epithelium covers a small area of roughly 10 to 15 cm, representing approximately 8–10% of the total internal nasal surface area.[34] The olfactory neuro epithelium is structurally distinct from the respiratory mucosa, consisting of three primary cellular components: bipolar olfactory receptor neurons (ORNs), sustentacular supporting cells, and basal stem cells.[35]

The olfactory receptor neurons are unique because they are modified, unmyelinated bipolar nerve cells that provide a direct, continuous structural link between the external environment and the central nervous system.[36] The apical end of each ORN features a single dendritic process that extends to the mucosal surface, terminating in an expanded olfactory knob that projects 10 to 20 non-motile, elongated cilia directly into the overlying protective mucus layer.[37] The basal ends of these ORNs taper into fine, unmyelinated axons.[38]

These individual axons cluster together into specialized anatomical bundles known as the fila olfactory.[39] These neural bundles travel upward, passing directly through the microscopic fenestrations of the bony cribriform plate to enter the cranial cavity, where they terminate and synapse directly within the complex glomerular structures of the olfactory bulb.[40]

Complementing this system is the trigeminal nerve pathway.[41] The respiratory and olfactory mucosa are heavily innervated by the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve.[42] The nerve endings of the trigeminal system do not enter the olfactory bulb; instead, they enter the cranium through the superior orbital fissure and the foramen

rotundum, providing a direct structural link into the caudal brain stem regions, specifically the pons, medulla, and spinal cord.[43]

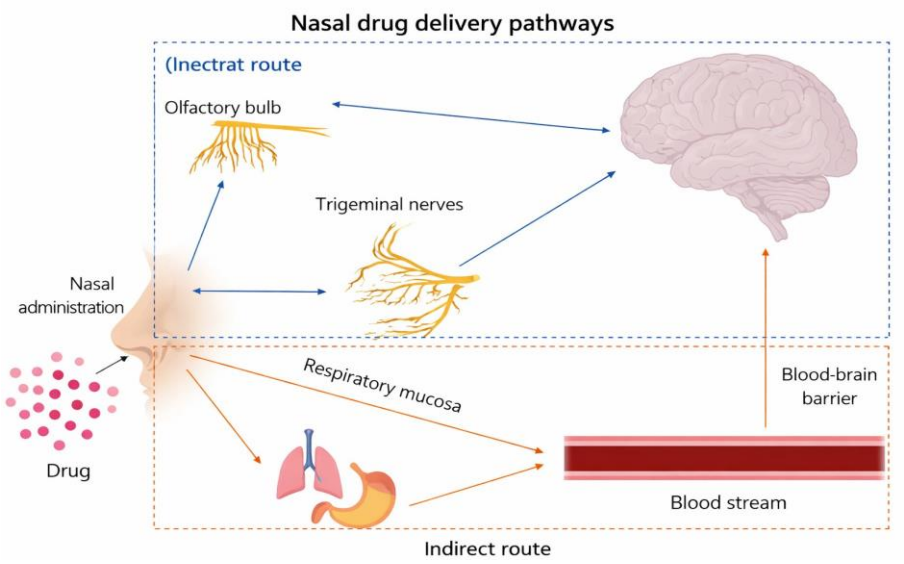


Figure 1: Direct neuro – peri neural pathway vs indirect systemic absorption route.

3.3 cellular mechanism of transcellular movement

When a stimuli-responsive *in situ* gel is successfully deposited onto the upper olfactory epithelium, the encapsulated therapeutic molecules utilize three distinct transport mechanisms to move from the mucosal surface into the cerebral compartments:

1. **The Intracellular Axonal Pathway:** This mechanism begins when drug molecules are internalized into the ORNs via receptor-mediated endocytosis, fluid-phase pinocytosis, or simple adsorptive endocytosis at the apical dendritic knob.[44] Once inside the cytoplasm, the molecules are packaged into vesicular carriers and transported via retrograde axonal transport along the unmyelinated axon fibers, moving across the cribriform plate to the olfactory bulb.[45] While this intracellular pathway successfully bypasses the BBB, it is inherently limited by slow transport kinetics, typically requiring hours to days for macromolecules to travel the length of the nerve fiber.[46]

2. **The Extracellular Perineural Pathway:** This represents the primary and most rapid transport track for N2B delivery.[47] The unmyelinated axons of the *fila olfactory* are enveloped by specialized glial cells known as olfactory ensheathing cells (OECs), which form distinct Perineural channels.[48] These Perineural sheaths contain extracellular fluid that is continuous with the subarachnoid space surrounding the brain.[49] Drug molecules can pass paracellularly across the olfactory epithelium and enter these Perineural spaces,

moving rapidly upward through the cribriform plate via passive diffusion and bulk fluid flow driven by respiratory pressure changes.[50] This pathway can deliver therapeutics into the CSF and cerebral hemispheres within minutes of nasal administration.[1]

3. **The Transcellular / Epithelial Diffusion Pathway:** Sustentacular supporting cells provide structural and metabolic support to the ORNs.[2] Small lipophilic molecules can partition directly across the apical membranes of these supporting cells, moving via passive transcellular diffusion into the underlying lamina propria.[3] From the lamina propria, the molecules can access the perineural spaces or enter the localized lymphatic drainage pathways that communicate directly with the cerebral subarachnoid space.[4]

4. Physiological barriers confronting intranasal delivery

While the olfactory and trigeminal networks provide a direct path to the brain, an intranasal administered drug faces robust physiological defense mechanisms designed to neutralize and eliminate foreign agents from the respiratory tract.[5]

4.1 The mucociliary clearance (MCC) bottleneck

The foremost kinetic barrier to successful N2B delivery is the mucociliary clearance apparatus.[6] The nasal mucosa is covered by a continuous, dynamic, bipartite viscoelastic mucus hydrogel blanket that ranges from 5 to 15 micrometers in thickness.[7] This mucus layer is structurally organized into two distinct physiological phases:

- **The Periciliary "Sol" Layer:** The lower layer is a low-viscosity aqueous fluid that surrounds the shafts of the ciliated epithelial cells, allowing them to beat freely with minimal resistance.[8]
- **The Overlying "Gel" Layer:** The upper layer is a highly viscoelastic hydrogel composed of highly cross-linked, high-molecular-weight mucin glycoproteins (primarily MUC5AC and MUC5B).[9] These mucins feature dense networks of oligosaccharide side chains that terminate in negatively charged sialic acid and sulfate groups, giving the entire mucus blanket a net anionic charge at physiological pH.[10]

The coordinated, metachronal waving motion of the epithelial cilia beats at a frequency of 10 to 15 Hz within the lower sol layer, driving the sticky upper gel layer backward toward the nasopharynx at a continuous linear velocity of approximately 5 to 6 mm/min.[11] Consequently, any conventional liquid formulation (such as simple nasal drops or aqueous sprays) instilled into the nasal cavity is mechanically swept out of the nasal passages and

pushed down into the esophagus within 15 to 20 minutes.[12] This brief residence time severely limits the window available for passive trans-mucosal diffusion, resulting in low and unpredictable bioavailability, particularly for macromolecular biologics.[13]

4.2 the enzymatic barrier (nasal first pass metabolism)

In addition to mechanical clearance, the nasal mucosa possesses a functional metabolic barrier, often termed "nasal first-pass metabolism".[14] Although its overall metabolic capacity is lower than that of the gastrointestinal tract or the liver, the nasal epithelium contains high concentrations of both phase I oxidative enzymes and phase II conjugating enzymes concentrated within the cellular cytoplasm of the sustentacular supporting cells.[15]

Table 1: major enzymatic barrier of human nasal mucosa and targeted drug classes.

Enzyme Classification	Primary Subcellular Localization	Targeted Therapeutic Classes / Substrates	Biochemical Impact on N2B Delivery Formulations	Ref
Aminopeptidases & Endopeptidases	Microvillar membrane, Apical cell boundary	Calcitonin, Insulin, Enkephalins, Neurotropic peptides	Rapid hydrolytic cleavage of peptide bonds; completely inactivates macromolecular peptide drugs prior to mucosal absorption.	[16]
Cytochrome P450 (CYP450) Monooxygenases	Endoplasmic reticulum of supporting cells	Nicotine, Cocaine, Benzodiazepines, Neuroleptics	Oxidative biotransformation (hydroxylation, dealkylation); degrades lipophilic small molecules during transcellular passage.	[17]
Carboxylesterase	Cytoplasmic fraction, Mucosal secretions	Ester-prodrugs, Soluble ester compounds	Rapid hydrolysis of ester linkages; can prematurely activate or degrade ester-based prodrugs within the nasal lumen.	[18]
Glutathione Enzyme Classification	Cytosol and Primary Subcellular Localization	Electrophilic Targeted Therapeutic Classes / Substrates	Conjugation of Biochemical Impact on N2B Delivery Formulations	[19]

4.3 physiochemical epithelial constraints

The rate of passive molecular diffusion across the single-cell epithelial boundary is strictly governed by the physicochemical properties of the therapeutic molecule, including its

molecular weight, lipophilicity, and ionization state.[25] The paracellular transport route between adjacent epithelial cells is tightly restricted by apical junctional complexes, including desmosomes, zonula occludens (tight junctions), and adherence junctions.[26] These cellular structures present an effective hydrodynamic pore radius of only 10 to 15 Å.[27]

As a result, large hydrophilic molecules with a molecular weight greater than 1000 Da exhibit poor paracellular permeation, typically yielding absolute bioavailability of less than 1% without the aid of specialized permeation enhancers or tight-junction modulators.[28]

Conversely, lipophilic small molecules can readily pass via the transcellular route by partitioning directly into the lipid bilayer of the epithelial cell membranes.[29] However, highly lipophilic drugs face a different obstacle: they are often poorly soluble in the aqueous nasal mucus.[30] This low solubility leads to rapid molecular aggregation and physical precipitation within the nasal lumen, making the drug susceptible to mechanical clearance via the MCC before transcellular partitioning can occur.[31] This underscores the necessity of using smart, stimuli-responsive Mucoadhesive *in situ* hydrogel matrices.[32]

5. chemistry and phase-transition dynamics of stimuli responsive polymer

The engineered utility of smart *in situ* gelling fluids relies on the selection of responsive polymers that undergo rapid, predictable, and reversible macro-structural phase transitions.[33]

These polymers are formulated as low-viscosity solutions at ambient room conditions (20–25°C), allowing for standard aerosolized administration via commercial nasal spray pumps.[34] When introduced into the nasal cavity, the polymers detect specific physiological changes in the microenvironment, triggering an immediate shift into a rigid, non-flowing viscoelastic hydrogel network.[35]

5.1 Thermoresponsive polymeric networks: hydrophobic Desolvation kinetics

Thermoresponsive systems represent the most widely used class of smart intranasal gels.[36] These matrices utilize polymers designed to display a Lower Critical Solution Temperature (LCST) tailored precisely between room storage temperature and the physiological temperature of the upper nasal vault (32–34°C).[37] At room temperature, the polymer chains exist as highly hydrated random coils.[38] The thermodynamic balance of the solution is dominated by strong hydrogen bonding between the water molecules and the hydrophilic domains of the polymer, which keeps the formulation in a free-flowing liquid state.[39]

When sprayed onto the nasal mucosa, the ambient temperature rises past the LCST, altering the system's thermodynamics.[40] The thermal energy disrupts the stabilizing water-polymer hydrogen bonds.[41] The surrounding water molecules lose their random orientation and form organized, cage-like clathrate structures around the hydrophobic segments of the polymer backbone, causing a decrease in system entropy.[42] To counteract this loss of entropy, the polymer chains undergo a conformational transition.[43] The hydrophobic domains self-assemble to minimize contact with the aqueous phase, driving desolvation and micellar aggregation.[44] As these micelles increase in concentration, they pack tightly together, culminating in a phase transition into a three-dimensional physical hydrogel.[45]

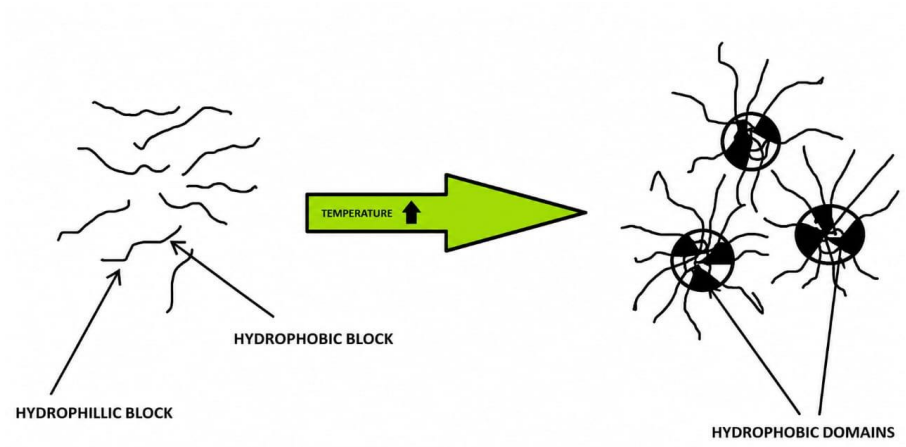


Figure 2: Phase-Transition Dynamic of Thermoresponsive Hydrogels.

The primary polymers used for thermoresponsive nasal gels are **Poloxamers** (Pluronic F-127 and F-68).[46] Poloxamers are non-ionic triblock copolymers arranged in a distinct linear sequence: poly (ethylene oxide)-poly(propylene oxide). The central PPO block is hydrophobic, while the flanking PEO chains are hydrophilic.[48] At a critical micelle concentration (CMC) and temperature, the PPO blocks self-assemble into an inner core, while the PEO blocks project outward to form a hydrated outer shell.[49]

For nasal applications, a concentration of 18% to 20% w/v of Poloxamer F-127 provides an ideal gelation temperature near 32°C.[50] However, pure Poloxamer hydrogels often suffer from low mechanical strength and are easily eroded by native nasal fluids.[1] To improve structural stability, they are typically blended with secondary Mucoadhesive polymers—such as hydroxypropyl methylcellulose (HPMC) or carbomers—to establish dense interpenetrating polymer networks (IPNs).[2]

5.2 ion activated system: cationic electrostatic cross linking

Ion-activated, or ionotropic, *in situ* gels trigger their phase transition by reacting with the endogenous cations present within the human nasal mucus layer.[3] The premier biopolymer for this mechanism is **Deacetylate Gellan Gum.**[4] Gellan gum is an anionic microbial exopolysaccharide consisting of a repeating tetra saccharide backbone: Beta-D-glucose, Beta-D-glucuronic acid, and Alpha-L-rhamnose.[5] In an aqueous, deionized environment at room temperature, Gellan gum molecules assume a highly flexible, disordered single-helix conformation.[6] The formulation maintains a low fluid viscosity due to mutual electrostatic repulsion between the un-ionized carboxylic acid side groups on the glucuronic acid subunits.[7] When atomized into the nasal cavity, the formulation mixes with native nasal fluid, exposing the polymer chains to ambient ions.[8] These ions shield the repulsive negative charges along the carbohydrate backbone.[9] This electrostatic stabilization allows the isolated single helices to aggregate into parallel, coaxial double-helical structures.[10]

Furthermore, divalent cations serve as direct intermolecular salt bridges.[11] They coordinate with the carboxylate zones of adjacent double helices, initiating extensive physical cross-linking that transforms the fluid into an elastic hydrogel matrix almost instantly.[12]

5.3 PH-triggered matrices: ionization-induced chain uncoiling

pH-responsive *in situ* formulations rely on polymers that feature ionizable functional groups along their primary structural backbone.[13] Poly (acrylic acid) polymers, commercially classified as **Carbopols** (such as Carbopol 934 and 974P), are the standard choice for this approach.[14] Carbopol solutions are maintained at an acidic pH (~4.0–5.0) during manufacturing, where the carboxylic acid groups remain largely protonated (COOH).[15] In this state, the polymer chains remain tightly coiled, displaying low fluid resistance suitable for fine droplet atomization.[16]

Upon entering the nasal cavity, the formulation encounters the higher physiological pH of the nasal fluid (~5.5–6.5).[17] This pH shift drives partial deprotonation, converting the carboxylic acid units into negatively charged carboxylate anions.[18] The sudden appearance of dense, localized negative charges triggers strong intramolecular electrostatic repulsions along the polymer backbone, forcing the coiled chain to rapidly uncoil into an extended structure.[19] This uncoiling promotes extensive interchain entanglement, leading to a rapid increase in viscosity and a stable gel phase.[20]

6. comprehensive structural analysis of Mucoadhesion mechanics

Mucoadhesion is the operational foundation that allows an *in situ* gel to successfully resist mucociliary clearance, maintaining the therapeutic payload against the olfactory region for extended periods.[21] This bio-interface phenomenon occurs via two sequential steps: the contact phase and the consolidation phase.[22]

6.1 The mechanical contact phase

The contact phase begins as the atomized fluid exits the spray nozzle, spreads over the irregular typography of the nasal mucosa, and wets the epithelial surface.[23] Spreading is dictated by the surface tension of the liquid and the wetting kinetics of the polymer matrix.[24] Efficient wetting maximizes the available surface area for subsequent molecular interactions.[25]

6.2 The consolidation phase and polymer interpenetration

Once contact is established, the consolidation phase begins via two key steps:

- **Macromolecular Chain Interdiffusion:** The uncoiled chains of the stimuli-responsive polymer diffuse physically into the highly elongated, tangled network of the host mucin glycoproteins.[26] This mutual chain Interdiffusion forms a physically blurred, intermingled interfacial boundary layer.[27]
- **Chemical Interfacial Bonding:** Following physical entanglement, the functional groups of the polymer establish secondary chemical bonds with the specific amino acid residues and oligosaccharide side chains of the mucin molecules.[28]

The primary molecular forces driving this consolidation include hydrogen bonding, electrostatic attraction, and hydrophobic interaction.[29]

6.3 polymeric architecture and Mucoadhesive performance

The chemical structure of the polymer dictates the overall strength of the Mucoadhesive bond:

- **Polyanions (Carbopol, Na-CMS):** These matrices utilize their high concentrations of carboxylic acid groups (COOH) to form extensive hydrogen bonds with the hydroxyl (OH) and amide groups of the mucin chains.[30]
- **Polycations (Chitosan):** Chitosan is a linear amino polysaccharide derived from the partial deacetylation of chitin.[31] In the mildly acidic nasal environment, its primary amine groups undergo protonation to form positively charged ammonium ions. These cationic centers establish strong electrostatic bonds with the negatively charged sialic acid

and sulfate residues present on the terminal branches of mucin proteins.[33] This electrostatic attraction creates a robust Mucoadhesive bond that reliably resists the mechanical shearing forces of ciliated clearance.[34]

Furthermore, chitosan provides a distinct functional advantage: it transiently opens epithelial tight junctions by interacting with protein components like claudin-5, safely increasing paracellular permeability for hydrophilic therapeutic payloads.[35]

7. safety, histopathological integrity and regulatory hurdles

Developing an effective intranasal *in situ* gel requires balancing strong permeation enhancement with preservation of the delicate nasal mucosa.[20] The respiratory and olfactoryepithelia are sensitive structures; chronic or repeated exposure to aggressive chemical penetration enhancers (such as high concentrations of synthetic surfactants, bile salts, or chelators) can cause tissue damage.[21] This damage can manifest as a loss of protective ciliated epithelial cells, structural shrinkage of the mucosal layers, structural vacuolation, or focal points of localized necrosis.[22]

Hence, a clinical candidate *in situ* gel must undergo formal *ex vivo* or *in vivo* nasal ciliotoxicity evaluations.[23] Following fixed-term dosing regimens, excised nasal tissues are subjected to sectioning and staining with Hematoxylin and Eosin (H&E) to confirm that the formulation maintains mucosal integrity without causing irreversible structural changes.[24]

Beyond cellular toxicity, there are significant physiological constraints on formulation design.[25] The maximum volume that can be comfortably administered into a single human nostril is strictly limited to 25–200 microliters.[26] Instilling larger volumes causes the fluid to drain into the pharynx, where it is swallowed, potentially causing systemic side effects and taste disturbances.[27]

This volume restriction requires that the therapeutic agent exhibit high solubility within the vehicle or be loaded at a high density within the embedded Nano carriers.[28] Furthermore, the formulation must be biocompatible with the native nasal fluid, maintaining an acceptable physiological pH range (5.5–6.5) and appropriate osmotic balance to prevent local irritation or reflex sneezing.[29]

From an industrial scale-up perspective, guaranteeing long-term physical and chemical stability within multi-dose nasal delivery devices presents a notable challenge.[30] For

thermoresponsive systems, the viscosity must remain stable during storage at colder refrigeration temperatures (4–8°C), during room-temperature shipping, and throughout patient use.[31] Sterility validation, preventing microbial growth within aqueous polymeric matrices, and ensuring consistent droplet size distribution upon aerosolization through commercial mechanical pump sprays are critical performance parameters required by regulatory bodies like the FDA and EMA before these systems can transition from preclinical models into human clinical trials.[32]

8. future perspective and advance architecture horizons

The next phase of innovation in intranasal *in situ* gels focuses on integrating smart, multi-responsive polymer chemistry with digital development technologies.[40] Current research is shifting toward **dual-responsive systems** that transition only when multiple physiological conditions are met simultaneously (e.g., combining thermoresponsive Poloxamer blocks with ion-activated Gellan gum).[41] This dual-trigger approach ensures that premature gelation does not occur inside the delivery device during storage in warm climates, as the sol-to-gel transformation requires both physiological temperatures and contact with the ions of the nasal mucus.[42]

Concurrently, researchers are adopting **Quality by Design (QbD)** frameworks and **Machine Learning (ML)** algorithms to optimize nasal formulations.[43] Rather than relying on traditional empirical trial-and-error, scientists deploy artificial neural networks (ANNs) and response surface methodologies to analyze complex multi-variable datasets.[44] These algorithms model how shifting polymer ratios impact critical quality attributes, including exact gelation temperature, gel strength, Mucoadhesive force, and *in vitro* drug release kinetics.[45] This digital approach accelerates the development of safe, highly optimized nasal drug delivery platforms.[46]

9. CONCLUSION

Stimuli-responsive Mucoadhesive *in situ* gels represent a significant advancement in non-invasive drug delivery for central nervous system disorders. By converting from a free-flowing liquid to a cohesive hydrogel matrix directly upon contact with the nasal mucosa, these systems overcome the key limitations of rapid mucociliary clearance and brief localized residence times. Integrating biocompatible Mucoadhesive polymers like chitosan, Gellan gum, and Poloxamer cross-linked networks provides extended retention at the upper olfactory neuroepithelium. This sustained contact drives efficient transport across direct nose-to-brain

pathways, bypassing the blood-brain barrier.

When combined with lipid or polymeric Nano carriers, these hybrid systems protect sensitive therapeutics from enzymatic degradation and improve trans-mucosal flux. Quantitative pharmacokinetic indicators, including elevated Drug-Targeting Indexes (DTI > 1.0) and high Direct Transport Percentages (DTP%), confirm the efficacy of this approach in preclinical models. As formulation design benefits from multi-responsive polymer chemistry and structured Quality by Design optimization, intranasal *in situ* gels are well-positioned to bridge the gap between discovery and clinical translation for neuro therapeutics.

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