

NANOCARRIER-LOADED THERMOSENSITIVE IN SITU GELS FOR DIRECT NOSE-TO-BRAIN DELIVERY OF ANTIPSYCHOTICS: A COMPREHENSIVE REVIEW

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Abstract: Treating severe psychiatric conditions like schizophrenia and bipolar disorder often hits major physiological roadblocks. Systemically administered drugs struggle to cross the blood-brain barrier, undergo heavy first-pass liver metabolism, and frequently trigger debilitating peripheral side effects, such as extrapyramidal symptoms and metabolic syndrome. Delivering medications intranasally offers an elegant alternative. By utilizing the olfactory and trigeminal nerve pathways, therapeutics can travel straight to the brain, completely avoiding systemic circulation. Yet, standard liquid nasal formulations face their own distinct hurdles: the nasal cavity has a highly restricted volume, many neurotherapeutics suffer from poor aqueous solubility, and protective mechanisms like rapid mucociliary clearance quickly wash the drugs away before they can be absorbed. A novel dual-component delivery system combining cyclodextrin-based nanosponges with thermosensitive, mucoadhesive in situ hydrogels presents a highly effective solution to these barriers. Because of their hyper-crosslinked, three-dimensional porous structure, nanosponges can trap large amounts of drug molecules. This review thoroughly examines the mechanisms making this targeted antipsychotic therapy possible, synthesizing the relevant neuroanatomy, encapsulation chemistry, polymer thermodynamics, and preclinical pharmacokinetic metrics that define the performance of nanosponge-loaded in situ gels.

Key words - Nose to brain delivery, Thermosensitive in situ gel, Nanosponges, Antipsychotics, Brain Targeting.

1. INTRODUCTION

Tens of millions of people worldwide suffer from debilitating neuropsychiatric illnesses, most notably schizophrenia, schizoaffective disorder, and acute bipolar mania. To manage these complex conditions, clinical practice currently relies on two primary pharmacological classes. The first includes typical, first-generation antipsychotics like haloperidol. The second comprises atypical, second-generation agents such as risperidone, olanzapine, clozapine, and aripiprazole. First-generation medications achieve their primary therapeutic effect by blocking dopamine D2 receptors throughout the mesolimbic pathway, which successfully diminishes positive psychotic symptoms. The major drawback, however, lies in their lack of selectivity. By simultaneously antagonizing D2 receptors in the nigrostriatal tract, these older drugs routinely trigger debilitating extrapyramidal motor side effects, including dystonia, parkinsonism, akathisia, and tardive dyskinesia. Second -generation agents were developed to overcome these motor complications while also addressing the negative symptoms of psychosis. They achieve this broader clinical profile through a dual mechanism, blocking both dopamine D2 and serotonin 5-HT_{2A} receptors. While this approach effectively spares the patient's motor function, it unfortunately trades one set of adverse events for another. Patients prescribed these atypical agents face a high risk of developing severe metabolic disturbances—such as significant weight gain, dyslipidemia, and insulin resistance—which ultimately drive long-term cardiovascular morbidity. [1,2]

Receptor-related adverse effects are only part of the problem. Conventional antipsychotics also suffer from fundamentally poor biopharmaceutical profiles. The majority fall into Class II or IV under the Biopharmaceutics Classification System (BCS). In practical terms, this indicates notoriously low aqueous solubility alongside heavy hepatic first-pass metabolism driven by cytochrome P450 enzymes, notably CYP2D6 and CYP3A4. To make matters worse, their systemic plasma protein binding routinely exceeds 90%. Even if an adequate concentration of the drug reaches the systemic circulation, it still confronts the blood-brain barrier (BBB) before it can access the brain parenchyma. This anatomical barricade is exceptionally formidable. It relies on non-fenestrated capillary endothelial cells locked tightly together by distinct junction complexes—specifically occludin, claudin-5, and zonula occludens-1. Supported by a surrounding layer of pericytes and astrocytic end-feet, this dense architecture essentially eliminates the paracellular transport of hydrophilic compounds. Lipophilic neurotherapeutics face a different, active defense mechanism. Luminal ATP-binding cassette efflux transporters, such as P-glycoprotein, continuously pump these lipid-soluble drugs right back into the capillary lumen. To counteract this relentless efflux and achieve therapeutic brain concentrations, clinicians are forced to prescribe elevated oral doses, which inevitably intensifies the patient's systemic toxicity. While long-acting injectable suspensions

were introduced to solve the problem of daily oral non-compliance, they introduce new clinical hurdles. These depot formulations are invasive, expensive, and characterized by extremely long terminal elimination half-lives. Because the medication clears from the body so slowly, doctors find it practically impossible to rapidly adjust a patient's dosage during an acute psychiatric crisis.[3] Delivering drugs directly from the nasal cavity to the brain offers a compelling, non-invasive alternative to systemic administration. By utilizing the trigeminal and olfactory nerve pathways, therapeutics can entirely bypass the blood-brain barrier while simultaneously escaping first-pass liver degradation. Yet, despite the obvious theoretical appeal of this route, conventional liquid nasal sprays have largely fallen short in clinical practice. The primary culprit is the nose's natural defense system: mucociliary clearance. The nasal cavity is lined with actively beating cilia that rhythmically sweep deposited liquids and foreign particles backward into the nasopharynx. Because of this highly efficient clearance mechanism, applied formulations are typically washed away within a mere 15 to 20 minutes, leaving very little time for drug absorption. Compounding this rapid washout is a strict anatomical constraint. A single nostril can only accommodate a fluid volume of roughly 150 to 200 microliters per dose. Because most antipsychotic compounds are notoriously insoluble in water, they simply cannot dissolve adequately in these minute pools of nasal fluid. As a result, the active pharmaceutical ingredients tend to precipitate out of the solution, which inevitably provokes local mucosal irritation rather than delivering a therapeutic effect.[4]

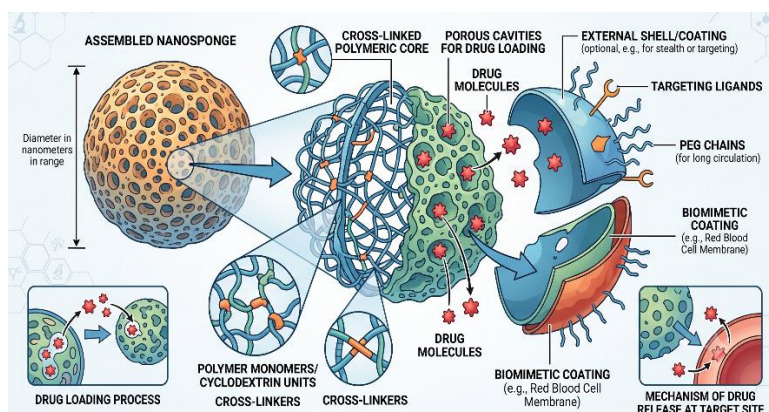


Figure 1: nanosponge

To overcome these exact physiological limitations, researchers have engineered an innovative dual-component platform: nanocarrier-loaded thermosensitive in situ gels. At the core of this system are cyclodextrin-based nanosponges. Thanks to their porous, hyper-crosslinked architecture, these tiny colloidal structures can successfully sequester hydrophobic medications deep within their internal cavities. This encapsulation process accomplishes much more than simply boosting the drug's solubility; it actively shields the fragile compound from enzymatic degradation while establishing a steady, sustained release profile. The second crucial element is the delivery vehicle itself. The drug-loaded nanosponges are suspended in a specialized thermoreversible matrix, typically formulated from poloxamer copolymers blended with mucoadhesive agents. While kept at ambient room temperatures (20–25 °C), the preparation behaves as a standard low-viscosity fluid, making it exceptionally easy to handle and aerosolize. The critical shift occurs directly upon administration. The instant this liquid contacts the warmer environment of the nasal mucosa (32–35 °C), it triggers a rapid structural transition, transforming the fluid spray into a resilient, bioadhesive hydrogel. By solidifying in place, the gel effectively fights off the sweeping motion of mucociliary clearance. It remains firmly anchored to the mucosal interface for an extended period, ultimately ensuring a prolonged and highly efficient therapeutic transit straight to the central nervous system.[5–7]

2. NEED OF THE STUDY.

Even with a wide array of antipsychotic medications currently available, successfully managing severe psychiatric illnesses remains a profound clinical challenge. The primary hurdle is medication non-adherence, a behavioral barrier that impacts more than 50% of all ambulatory patients. When individuals take their oral prescriptions inconsistently, it creates chaotic fluctuations in their plasma drug levels. These erratic peaks and troughs not only drive receptor desensitization but also trigger acute breakthrough psychotic episodes that routinely end in hospital readmission. Long-acting intramuscular injections offer a partial fix for this widespread non-compliance, yet they carry distinct clinical drawbacks. Many patients actively resist these therapies simply because the injections are painful and invasive. Furthermore, the prolonged systemic presence of these depot formulations creates a serious safety liability: if a patient suddenly develops a severe adverse reaction, physicians cannot rapidly halt the treatment. Ultimately, both traditional oral and parenteral administration routes share a fundamental biopharmaceutical flaw—they unavoidably flood the entire body with high drug concentrations. This massive systemic exposure is the direct cause of severe, treatment-limiting side effects. Depending on the drug, this ranges from the debilitating motor toxicities seen with typical agents like haloperidol, to the extensive cardiometabolic dysfunction caused by atypical options such as clozapine, olanzapine, and risperidone.[8]

While delivering drugs through the nasal cavity successfully circumvents hepatic first-pass metabolism and systemic vascular clearance, relying on standard aqueous solutions or basic suspensions rarely achieves therapeutic drug concentrations in the brain. The primary obstacle is the body's relentless mucociliary clearance mechanism. This natural sweeping action rapidly pushes liquid droplets backward into the nasopharynx where they are inevitably swallowed. Consequently, what was intended as a targeted nasal therapy essentially devolves into unpredictable gastrointestinal absorption. Furthermore, the sheer lack of available moisture in the nasal cavity—which holds a meager 100 to 200 microliters of fluid—creates a major solubility bottleneck for hydrophobic

compounds. Instead of dissolving smoothly, these poorly soluble drugs tend to precipitate out of the liquid, provoking localized tissue irritation and guaranteeing highly inconsistent dosage delivery.[9,10]

To successfully navigate these formidable anatomical and biopharmaceutical hurdles, an ideal drug delivery platform must be able to multitask. Specifically, it needs to simultaneously dissolve the active compound, shield it from degradation, anchor firmly to the nasal lining, and strictly govern the release of the medication over time. Polymeric nanosponges elegantly handle the first two requirements. By locking poorly soluble, lipophilic molecules deep inside complex supramolecular cages, they keep the therapeutic payload chemically stable and well-dispersed. However, protecting the drug is only half the battle; it must also stay in place. To solve the retention problem, these nanocarriers are embedded within a thermosensitive *in situ* gelling matrix. The instant this liquid formulation makes contact with the warm neuroepithelium, it undergoes a rapid fluid-to-gel phase shift. This immediate solidification acts as a physical anchor, effectively shutting down the washout normally caused by mucociliary clearance. Given how rapidly this dual-action technology is evolving, there is a pressing need to systematically map out the current landscape of the research. Therefore, this review aims to consolidate the underlying polymer chemistry, critical formulation variables, neuroanatomical transport routes, and emerging preclinical data surrounding nanosponge-loaded *in situ* gels. By synthesizing these diverse elements, this paper provides a comprehensive framework intended to accelerate the development of next-generation, non-invasive psychiatric therapies.[11]

3. RESEARCH METHODOLOGY

3.1. Protocol Architecture and Systematic Review Design

To ensure a rigorous and transparent analytical approach, we anchored our methodology to the established Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We did, however, tailor these standard directives slightly to better accommodate the highly specialized nuances of pharmaceutical formulation science and preclinical pharmacokinetic testing. Before launching the literature retrieval phase, we established a strict preliminary protocol. This critical planning step allowed us to clearly define our core research questions, lock in the exact search parameters, dictate which specific delivery platforms would qualify for inclusion, and select the quantitative metrics necessary to evaluate formulation performance. Ultimately, our primary investigation honed in on a highly specific drug delivery strategy. We closely examined the technique of sequestering lipophilic antipsychotic medications inside cyclodextrin-engineered nanosponges. Going a step further, we analyzed how these loaded nanocarriers behave once suspended within thermoreversible *in situ* polymeric matrices. Our main objective was to evaluate their overall biopharmaceutical performance, paying close attention to how effectively they navigate the complex physiological hurdles of the nasal epithelium and neuronal transport pathways.[12]

3.2. Information Sources and Search Strategy

To build a robust foundation of evidence, we queried several premier databases spanning the biomedical, pharmaceutical, and chemical sciences. The primary digital platforms utilized included PubMed/MEDLINE, ScienceDirect, Scopus, Web of Science (Clarivate Analytics), Google Scholar, and the Cochrane Central Register of Controlled Trials. We restricted our chronological window to peer-reviewed articles published between January 2000 and the present. We deliberately selected this timeframe to bridge the gap between early, foundational discoveries in polymer chemistry and today's cutting-edge developments in neuropharmacokinetics. To mine these extensive databases efficiently, we developed a highly targeted search syntax. We paired standardized Medical Subject Headings (MeSH) with highly specific free-text keywords, integrating them using classic Boolean logic (AND, OR, NOT). To keep the retrieval process organized and exhaustive, we divided our search strings into four distinct conceptual tiers:

Tier 1: The Nanocarrier Platform. To capture literature focusing specifically on the structural architecture of the delivery vesicles, we applied the following query: ("nanosponge" OR "nanosponges" OR "cyclodextrin nanosponge" OR "cross-linked cyclodextrin" OR "polymeric nanocarrier").

Tier 2: The Polymeric Gelling Vehicle. To isolate studies detailing the stimuli-responsive, rheological matrices used to suspend the nanocarriers, we searched: ("in-situ gel" OR "thermosensitive gel" OR "thermoreversible hydrogel" OR "temperature-induced gel" OR "poloxamer" OR "pluronic F127" OR "mucoadhesive nasal gel").

Tier 3: Route of Administration and Physiological Pathways. To guarantee the anatomical focus remained strictly on direct transport to the central nervous system, we utilized: ("intranasal" OR "nose-to-brain" OR "olfactory pathway" OR "trigeminal pathway" OR "transnasal delivery" OR "cribriform plate").

Tier 4: Therapeutic Class and Specific Pharmaceutical Agents. Finally, to restrict the clinical scope to severe psychiatric management and specific drug compounds, our search included: ("antipsychotic" OR "schizophrenia" OR "bipolar disorder" OR "risperidone" OR "aripiprazole" OR "haloperidol" OR "olanzapine" OR "clozapine" OR "quetiapine" OR "ziprasidone").

To synthesize these conceptual tiers across the various search engines, we deployed the following master Boolean query: ("nanosponge" OR "cyclodextrin nanosponge") AND ("in-situ gel" OR "thermosensitive" OR "poloxamer") AND ("intranasal" OR "nose-to-brain") AND ("antipsychotic" OR "schizophrenia" OR "risperidone" OR "aripiprazole" OR "haloperidol" OR "olanzapine").

Because algorithmic database searches can occasionally miss relevant literature, we supplemented our digital retrieval with a meticulous manual approach. We rigorously combed through the reference lists of pertinent systematic reviews and pivotal primary articles to identify older, foundational work (backward citation tracking). Simultaneously, we investigated newer papers that cited these core manuscripts (forward citation tracking). This dual-pronged strategy ensured that no eligible formulation studies were inadvertently overlooked during the initial screening process.[13]

3.3. Eligibility and Study Selection Criteria

To rigorously filter the retrieved literature, we established a strict set of inclusion and exclusion parameters. We designed these filters specifically to isolate studies that thoroughly evaluated the formulation architecture, rheological properties, and ultimate central nervous system biodistribution of the delivery systems.

Table 1: Eligibility and Study Selection Criteria

Domain	Inclusion Parameters[14,15]	Exclusion Parameters[16]
Therapeutic Cargo	We required the use of typical (first-generation) or atypical (second-generation) antipsychotics, such as haloperidol, clozapine, aripiprazole, risperidone, or olanzapine.	We rejected studies utilizing non-psychoactive CNS drugs, peripheral analgesics, or poorly characterized botanical extracts.
Nanocarrier Architecture	Formulations had to feature polymeric or cyclodextrin-engineered nanosponges formulated through quasi-emulsion diffusion, crosslinking, or solvent evaporation techniques.	We excluded basic, unencapsulated crude suspensions, macro-scale particulate carriers, and simple inclusion complexes lacking a true crosslinked network.
Gel Matrix	The delivery vehicle needed to be a stimuli-responsive hydrogel capable of a thermoreversible sol-to-gel transition specifically at nasal physiological temperatures (30–36 °C).	Standard non-gelling nasal drops, static ointments, and any liquid formulations completely lacking bioadhesive polymers were dismissed.
Delivery Route	The research had to explicitly investigate intranasal administration aimed at direct nose-to-brain translocation.	Investigations strictly focused on oral, ocular, transdermal, or intravenous routes—unless they included a direct transnasal comparator arm—were removed from consideration.
Characterization Metrics	Eligible manuscripts provided comprehensive physical characterizations (e.g., entrapment efficiency, zeta potential, particle size) alongside concrete gelation kinetics and pharmacokinetic/permeation profiles.	We omitted papers that failed to clearly report their fabrication protocols or lacked hard, quantitative evaluation data.
Publication Type	We limited our scope to peer-reviewed, original research manuscripts and high-impact mechanistic evaluations published in English.	Non-peer-reviewed notes, brief conference abstracts missing methodological details, duplicate data sets, and editorial letters were discarded.

3.4. Screening Protocol and Data Extraction Process

To maintain objectivity and thoroughness, two independent researchers conducted the literature screening using a structured, two-stage pipeline.

Phase One: Title and Abstract Screening. Once duplicate records were purged from the initial search pool, the reviewers independently evaluated the remaining titles and abstracts against our strict eligibility parameters. This first pass allowed us to swiftly eliminate clearly irrelevant literature, including research focused on standard oral tablets, unformulated drug solutions, or simple non-crosslinked carrier systems.

Phase Two: Full-Text Evaluation. Following the initial purge, we retrieved the complete manuscripts for all remaining candidates and subjected them to a deep, granular analysis. In instances where the reviewers disagreed on a paper's methodological integrity or its overall alignment with the inclusion criteria, they deliberated the specific discrepancies until a mutual consensus was achieved. To systematically organize our findings, we built a customized data extraction matrix. This dedicated spreadsheet allowed us to meticulously record both the qualitative design elements of each formulation and their hard quantitative outcomes.

• **Nanosponge Architecture.** we extracted a wealth of structural and chemical data:

Chemical Composition: We tracked the specific polymer backbone (such as native β -cyclodextrin or HP- β -CD) alongside the choice of chemical crosslinker, whether that was diphenyl carbonate, carbonyldiimidazole, or pyromellitic dianhydride.

Fabrication Details: We documented the exact synthesis techniques and the stoichiometric ratios utilized by the researchers.

Physical Characterization: To assess the physical profile of the nanocarriers, we recorded critical metrics like the hydrodynamic particle size, zeta potential, polydispersity index (PDI), and the ultimate drug entrapment efficiency (EE%).

• **Hydrogel Matrix Characteristics:** For the delivery vehicle itself, we captured the specific concentrations of the foundational thermogelling agents—typically Poloxamer 188 or Poloxamer 407. We also noted the integration of secondary bioadhesive polymers, such as Carbopol, chitosan, or hydroxypropyl methylcellulose. To fully understand the thermodynamic and rheological behavior of these formulations, we extracted their sol-gel phase transition temperature ($T_{\text{sol-gel}}$) and total gelation time, along with dynamic viscosity readings taken at both room temperature (25 °C) and physiological temperature (35 °C). Finally, we logged the mucoadhesive detachment force to assess how firmly the gel anchors to the nasal mucosa.

• **Ex Vivo Permeation and In Vitro Release:** To evaluate how the active pharmaceutical ingredient escapes the matrix and crosses biological barriers, we documented the exact dissolution testing parameters alongside the subsequent release rate profiles. We paid close attention to the mathematical kinetic models used to explain this release mechanism, specifically looking at how studies applied Korsmeyer-Peppas or Higuchi models. Additionally, we gathered trans-membrane transport data, primarily focusing on the apparent permeability coefficients (K_p) and the steady-state mucosal permeation flux (J_{ss}) measured across excised tissue samples.

• **In Vivo Preclinical Pharmacokinetics:** The ultimate measure of formulation success relies on live-animal efficacy. In this final domain, we recorded the specific animal models chosen and the exact dosing regimens administered. From there, we pulled a

comprehensive suite of pharmacokinetic metrics. This included tracking the peak cerebral concentration ($C_{\max}$) and the time required to achieve that peak ($T_{\max}$). We also extracted the mean residence time (MRT), terminal elimination half-life ($t_{1/2}$), and the overall exposure quantified by the area under both the plasma and cerebral concentration-time curves (AUC_{0-t} and $AUC_{0-\infty}$). [17,18]

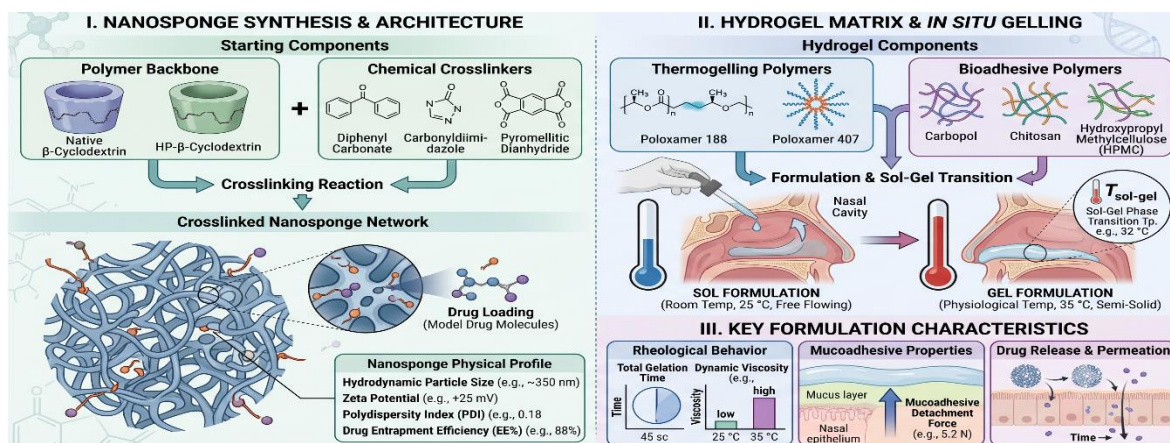


Figure 2: conceptual architecture and characterization of nanosponge-based in situ nasal gel

3.5 Pharmacokinetic and Biopharmaceutical Mathematical Models

A crucial question when evaluating these advanced formulations is determining their exact route of transport into the central nervous system. Specifically, researchers must prove that the drug is actively traveling along the direct olfactory and trigeminal nerve pathways, rather than simply absorbing into the systemic bloodstream and crossing the blood-brain barrier in the traditional manner. To verify this direct, targeted translocation, the extracted pharmacokinetic data were assessed against widely established quantitative indices:

Drug Targeting Efficiency (DTE%): This fundamental metric quantifies the formulation's capacity for brain targeting. It does so by comparing how much of the therapeutic agent accumulates in the cerebral parenchyma following intranasal administration against the baseline accumulation observed after standard intravenous injection.

$$DTE\% = \frac{\left(\frac{AUC_{0-t, \text{brain}}}{AUC_{0-t, \text{plasma}}} \right)_{IN}}{\left(\frac{AUC_{0-t, \text{brain}}}{AUC_{0-t, \text{plasma}}} \right)_{IV}} \times 100$$

In practical terms, achieving a DTE% that exceeds 100% serves as confirmation of successful targeting. It demonstrates that the intranasally applied therapeutic actively favors localization within the brain tissue rather than merely dispersing throughout the systemic vascular network.

Direct Nose-to-Brain Transport Percentage (DTP%): Going a step further than overall targeting efficiency, this metric isolates the exact fraction of the dose that bypasses the bloodstream entirely. It calculates the proportion of the therapeutic agent that reaches the central nervous system exclusively through direct neuronal corridors—specifically the olfactory and trigeminal tracts—relative to the total drug concentration found in the brain.

$$DTP\% = \frac{B_{IN} - B_x}{B_{IN}} \times 100$$

Within this framework, the B_{IN} variable denotes the total overall drug exposure within the brain following nasal administration (quantified as $AUC_{0-t, \text{brain}}(IN)$). In contrast, B_x accounts for the indirect pathway, representing the specific fraction of brain exposure that originated from systemic absorption and subsequently forced its way across the blood-brain barrier.

$$B_x = \frac{B_{IV}}{P_{IV}} \times P_{IN} = \frac{AUC_{0-t, \text{brain}}(IV)}{AUC_{0-t, \text{plasma}}(IV)} \times AUC_{0-t, \text{plasma}}(IN)$$

When the resulting DTP% registers as a positive value (between 0 and 100%), it provides definitive proof that the drug successfully utilized direct trans-cirbiform neuronal transport. More importantly, if this metric climbs above the 50% threshold, it confirms a critical biopharmaceutical milestone: the primary route of central nervous system entry was entirely direct, meaning the vast majority of the dose effectively bypassed the systemic vascular network. [19]

In Vitro Release Kinetics Modeling:

To map out exactly how the drug escapes the internal cavities of the nanosponge and subsequently navigates through the surrounding thermoreversible gel, researchers rely on mathematical modeling. Specifically, they fit the experimental dissolution data to the Korsmeyer-Peppas power law equation.

Within this mathematical framework, the ratio M_t / M_∞ represents the specific fraction of the therapeutic agent that has been liberated by a given time point t . The variable KKP functions as a structural kinetic constant tied directly to the delivery matrix, while n serves as the critical diffusional exponent.

The precise value of n essentially tells the story of the underlying release mechanism, particularly for matrix or cylindrical systems:

- **Standard Diffusion ($n < 0.45$):** A low exponent indicates quasi-Fickian diffusion, meaning the drug simply migrates through the matrix based on a standard concentration gradient.
- **Anomalous Transport ($0.45 < n < 0.89$):** Falling into this intermediate range points to non-Fickian transport. In this scenario, the release is fueled simultaneously by two forces: standard molecular diffusion and the physical swelling of the hydrogel network.
- **Polymer Relaxation ($n > 0.89$):** At this upper threshold, the system shifts into Case-II transport. Here, the drug is expelled primarily because the polymer chains comprising the gel are structurally relaxing and uncoiling over time.

$$\frac{M_t}{M_\infty} = K_{KP} \cdot t^n$$

3.6. Quality Appraisal and Risk of Bias Assessment

To ensure the fundamental integrity of our findings, we subjected every included manuscript to a rigorous quality control evaluation. Rather than taking published results at face value, we systematically assessed the methodological soundness and overall reproducibility of the preclinical experiments. We anchored this appraisal process to established benchmarks within pharmaceutical nanotechnology, guaranteeing that any underlying biases or experimental blind spots were identified prior to data synthesis.

Physicochemical Robustness: We scrutinized exactly how investigators verified their structural data. This meant checking if dynamic light scattering equipment was properly calibrated and whether the formulation's surface morphology was visually confirmed using either transmission or scanning electron microscopy (TEM/SEM). Furthermore, we required studies to rigorously validate the solid-state characteristics of their matrices through a combination of differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FTIR). Lastly, we ensured that the quantitative chromatographic assays (such as HPLC or UPLC) demonstrated absolute analytical specificity for the active drug.

Methodological Transparency: Because experimental replicability hinges on precise reporting, we evaluated whether authors maintained strict consistency across their formulation variables. We paid special attention to whether they explicitly published their exact crosslinker-to-monomer stoichiometric ratios. We also checked for clear, step-by-step details regarding the cold-method techniques used for poloxamer dispersion, as well as the specific environmental conditions maintained while recording sol-to-gel phase transition temperatures.

Biological and Analytical Validity: For preclinical models, transparency in biological sourcing is paramount. We verified that researchers fully disclosed their *ex vivo* mucosal tissue origins—whether they relied on bovine, porcine, or sheep nasal membranes—and clearly explained their protocols for preserving tissue viability during permeation testing. Finally, we confirmed that all *in vivo* animal trials operated under explicit ethical review board approval and employed rigorous, extended pharmacokinetic sampling schedules capable of accurately capturing terminal elimination kinetics.

4. RESULTS AND DISCUSSION

4.1 Physiological Mechanisms and Pathways of Direct Nose-to-Brain Translocation

When a therapeutic is administered into the nasal cavity, it essentially faces an anatomical fork in the road: it can reach the cerebral parenchyma by hitching a ride on the systemic vasculature, or it can migrate straight down dedicated neural corridors. If the drug absorbs via the indirect systemic route, it must first permeate the respiratory mucosal lining and drain into the local venous plexuses. From there, it is swept down into the internal jugular vein, circulated through the heart, and finally pushed up into the cerebral capillaries. Unfortunately, this circuitous journey forces the active molecule to run a severe systemic gauntlet. Before it even attempts to penetrate the formidable blood-brain barrier (BBB), the drug is aggressively degraded by hepatic first-pass metabolism, filtered out by peripheral clearance mechanisms, and actively rejected by vascular efflux pumps. Conversely, targeted direct nose-to-brain delivery completely bypasses this systemic detour. By exploiting the unique, exposed anatomy of the olfactory neuroepithelium and the trigeminal sensory nerve pathways, formulations can utilize a physical, unobstructed anatomical bridge that directly links the external nasal environment straight into the central nervous system.

Nestled high within the upper nasal vault, the olfactory epithelium serves as a critical anatomical gateway, wrapping seamlessly over the superior turbinate and the porous cribriform plate of the ethmoid bone. This highly specialized mucosal tissue is structurally supported by a tri-cellular matrix, comprising regenerative basal cells, architectural sustentacular cells, and the primary conduits for central nervous system entry: bipolar olfactory receptor neurons. The physical architecture of these sensory neurons is uniquely suited for capturing molecules from the environment. On their apical surface, they project dendritic bulbs that thrust non-motile cilia directly into the overlying mucosal fluid. At their opposite basal pole, their axons merge to form the fila olfactoria—a dense network of unmyelinated nerve bundles. These axonal tracts act as a biological wiring system, threading their way up through the perforated, sieve-like bone of the cribriform plate to synapse directly inside the olfactory bulb.

When a drug formulation attempts to navigate this complex neuroepithelial checkpoint, it typically relies on one of two distinct translocation mechanisms:

The Intracellular (Axonal) Pathway: This route operates entirely within the sensory neuron itself. The process begins at the exposed dendritic membranes, where the therapeutic agent is internalized via endocytosis. Once packaged safely inside the cell, the drug payload embarks on a retrograde journey—essentially traveling backward along the internal cytoskeletal architecture of the olfactory nerve bundles until it is finally deposited into the olfactory bulb. While this highly specific mechanism is well-suited for ferrying bulky macromolecular ligands, it suffers from a severe kinetic bottleneck. Because the drug's delivery relies entirely on the

inherently sluggish pace of biological axonal transport, this pathway often requires several hours, or sometimes even entire days, to accumulate clinically viable drug concentrations within the central nervous system.

The Extracellular (Perineural) Pathway: In stark contrast to the slow intracellular route, this alternative mechanism capitalizes on bulk fluid dynamics. Instead of breaching the cell membrane, therapeutic nanoparticles navigate the open perineural clefts that run parallel to the olfactory nerve sheaths and the local vascular networks of the lamina propria. This transport is far from passive; the nanocarriers are actively propelled forward by the rhythmic mechanical force of arterial pulsations combined with shifting hydrostatic pressure gradients. Swept along by these underlying currents, the drug particles flush through the lamina propria, slip past the porous cribriform plate via the protective perineural channels, and empty directly into the cerebrospinal fluid (CSF) pooled within the subarachnoid space. Once safely deposited in the CSF, the brain's convective glymphatic system takes over, rapidly dispersing the therapeutic payload throughout the broader cerebral architecture. Because it completely bypasses the cellular internalization bottleneck, this fast-flowing extracellular corridor stands as the dominant, high-yield route for delivering nanocarriers to the brain.

To supplement the olfactory route, formulations can also exploit the expansive trigeminal sensory network. The vast majority of the nasal cavity—encompassing roughly 85% of its total surface area—is lined by respiratory epithelium. This massive mucosal territory is heavily innervated by the fifth cranial nerve, specifically relying on its ophthalmic (V_1) and maxillary (V_2) branches.

These sensory nerve fibers provide an alternative anatomical backdoor into the cranial vault. The fibers thread their way through distinct bony openings, namely the superior orbital fissure and the foramen rotundum. After converging at the trigeminal ganglion, this neural highway plugs directly into the brainstem at the level of the pons.

By utilizing extracellular perineural transport along these trigeminal axonal branches, drug molecules can be channeled straight to the more posterior and caudal sectors of the brain, bypassing systemic circulation entirely to reach critical structures like the cerebellum, medulla, and pons.

Ultimately, it is the synergistic use of both these neural corridors that makes intranasal delivery so powerful for psychiatric applications. While the olfactory network efficiently handles rapid delivery to rostral targets such as the striatum and frontal cortex, the trigeminal system ensures deep caudal penetration. Working in tandem, they guarantee a comprehensive and widespread therapeutic distribution across the entire central nervous system.

To definitively measure the success of this delivery strategy—and to prove that the therapeutic agent utilized direct neuronal transit rather than simply leaking into the systemic circulation to cross the BBB—investigators rely on two critical pharmacokinetic benchmarks: the Drug Targeting Efficiency (DTE%) and the Direct Nose-to-Brain Transport Percentage (DTP%).^[20]

The Drug Targeting Efficiency index essentially serves as a comparative performance ratio. It measures how intensely the active compound accumulates within cerebral tissue relative to the systemic bloodstream, contrasting the intranasal (IN) delivery outcomes directly against a standard intravenous (IV) baseline.

When evaluating preclinical success, the 100% mark represents the critical threshold. Any DTE% value that exceeds this baseline confirms that the nasal formulation successfully prioritized brain localization, effectively steering the therapeutic payload toward the central nervous system rather than allowing it to be diluted across the general vascular network.^[21,22]

The Direct Nose-to-Brain Transport Percentage provides a more granular look at formulation efficacy by isolating the exact fraction of the therapeutic that successfully utilized direct neural pathways. It achieves this level of specificity by mathematically stripping away any secondary drug accumulation that resulted from peripheral systemic absorption across the blood-brain barrier

$$DTP\% = \frac{B_{IN} - B_x}{B_{IN}} \times 100$$

To break down the mechanics of the formula, the B_{IN} parameter captures the total extent of drug exposure in the brain after nasal application, formally measured as the area under the curve ($AUC_{0-t, \text{brain (IN)}}$). Its counterpart, B_x , acts as a vital systemic correction factor. It estimates the precise fraction of that brain exposure resulting from the drug leaking into the bloodstream and eventually crossing the blood-brain barrier. This indirect vascular contribution is derived mathematically by cross-referencing intravenous (IV) and intranasal (IN) plasma profiles against brain accumulation:

$$B_x = \frac{B_{IV}}{P_{IV}} \times P_{IN} = \frac{AUC_{0-t, \text{brain (IV)}}}{AUC_{0-t, \text{plasma (IV)}}} \times AUC_{0-t, \text{plasma (IN)}}$$

Interpreting the final output is straightforward. Any positive DTP% reading confirms that at least a portion of the therapeutic agent successfully utilized the direct trans-cribriform neural pathway. However, breaching the 50% mark is the true indicator of formulation success, as it demonstrates that the engineered delivery system effectively forced the lion's share of its payload through non-vascular corridors.^[23]

4.2 Nanosponge Architecture and Drug Entrapment Mechanics

Fundamentally, nanosponges operate as solid, highly crosslinked colloidal frameworks riddled with internal nanoscale cavities. They stand apart from traditional hollow lipid vesicles or simple, single-ring cyclodextrin complexes by assembling into a robust, three-dimensional polymeric mesh. This intricate, sponge-like topology is highly versatile, allowing the matrix to simultaneously house both hydrophilic and lipophilic molecules. It achieves this broad drug compatibility by leveraging a dual entrapment strategy—trapping therapeutics via classical direct cavity inclusion while concurrently capturing them within the broader interstitial spaces of the polymer web.

At their core, these pharmaceutical carriers rely on a foundation of cyclic oligosaccharides. Researchers primarily build these networks using either the native β -cyclodextrin (β -CD) macrocycle or engineered derivatives like 2-hydroxypropyl- β -cyclodextrin (HP- β -CD).

Looking closely at the native beta-CD architecture, the ring is constructed from seven D-glucopyranose units stitched together by α -(1,4)} glycosidic bonds. This molecular arrangement naturally folds into a truncated cone. The resulting geometry is highly

functional, presenting a hydrophilic outer shell that interacts easily with aqueous environments, while concealing a distinctively lipophilic inner chamber.

Dimensionally, this internal pocket measures between 6.0 and 6.5 Å across, yielding a total volumetric capacity of roughly 262 Å³. Crucially, this specific spatial footprint perfectly accommodates the bulky, fat-soluble molecular frameworks typical of modern antipsychotic drugs.[24]

To transform these highly soluble monomers into resilient, insoluble nanoparticles, researchers must chemically bridge the individual cyclodextrin rings. This structural conversion is driven by polyfunctional crosslinking agents that actively target the available primary (C6) and secondary (C2, C3) hydroxyl groups situated along the upper and lower rims of the macrocycle.

The specific choice of crosslinker fundamentally dictates the chemical character and structural integrity of the resulting matrix:

Carbonyl Linkers: Deploying agents like diphenyl carbonate (DPC) or carbonyldiimidazole (CDI) yields a network stitched together by carbonate ester linkages.

Dianhydride and Dicarboxylic Linkers: Utilizing agents such as pyromellitic dianhydride (PMDA) weaves a more complex web of carboxylate and ester bridges throughout the scaffold.

Epoxide Crosslinkers: When the reaction is driven under alkaline conditions, agents like epichlorohydrin can be introduced to forge highly stable ether bonds.

Beyond simply selecting the linker, formulators heavily scrutinize the stoichiometric balance of the reaction. By precisely tuning the molar ratio of crosslinker to cyclodextrin—typically dialing it in anywhere between 1:2 and 1:8—investigators gain direct command over the physical architecture of the nanosponge. This critical ratio dictates the final mesh density, modulates the polymer's overall swelling capacity, fine-tunes the internal pore diameters, and ultimately governs the kinetic release rate of the encapsulated therapeutic payload.

To physically construct these nanocarriers, formulators deploy a variety of synthetic strategies. While modern ultrasound- or microwave-assisted protocols and quasi-emulsion solvent diffusion techniques are increasingly utilized, classic solvent condensation remains a foundational approach.

When executing a solvent condensation synthesis, the procedure begins by completely solubilizing the beta-CD monomer within an anhydrous polar aprotic environment—typically relying on robust solvents like dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). Once the initial solution is prepped, the chosen crosslinking agent (such as DPC or CDI) is introduced directly into the reactor.

The system is then subjected to a sustained reflux, with temperatures held precisely between 80 °C and 100 °C. This thermal incubation is allowed to run for anywhere from 4 to 24 hours, ensuring the polymerization cascade runs to absolute completion. Finally, the newly formed polymer mass must be rigorously purified. To strip away any toxic, unreacted starting materials or lingering solvent, the crude gel undergoes exhaustive Soxhlet extraction using either acetone or ethanol, culminating in a thorough vacuum drying phase to yield the purified, solid nanosponge matrix.

For the quasi-emulsion solvent diffusion approach, the synthesis relies heavily on controlled phase separation. Researchers begin by co-dissolving the target antipsychotic agent, the beta-CD monomer, and a supportive hydrophobic polymer—such as ethylcellulose—directly into a highly volatile organic solvent like acetone or dichloromethane.

This organic mixture is then carefully titrated into a larger aqueous bath that has been pre-treated with a stabilizing surfactant, typically polyvinyl alcohol (PVA, held strictly between 0.5% and 2.0% w/v). By subjecting this two-phase system to high-shear homogenization, the organic droplets are aggressively dispersed throughout the water. As the volatile solvent naturally flashes off and evaporates out of the emulsion, the suspended polymer matrix rapidly precipitates and hardens, locking the components together into the signature porous architecture of the nanosponge.

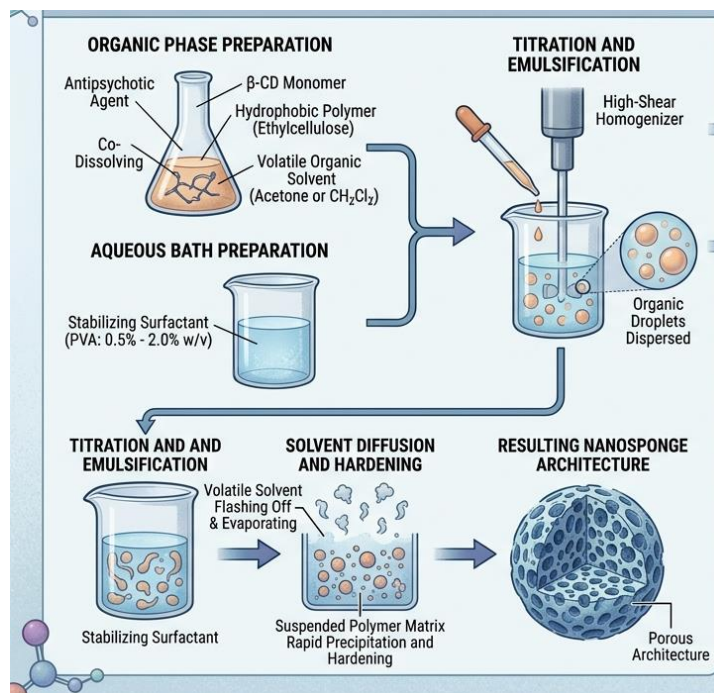


Figure 3 : quasi emulsion solvent diffusion

For those seeking to optimize manufacturing efficiency, modern ultrasound- and microwave-assisted protocols offer a high-energy alternative. By bombarding the reaction vessel with targeted sonochemical or microwave energy, these techniques drastically accelerate the crosslinking kinetics. This compresses polymerization cascades that traditionally took hours into a matter of minutes. Beyond simply saving time, this intense, uniform energetic input tightly controls the nucleation process, ultimately yielding significantly smaller, highly homogenous nanoparticle populations characterized by exceptionally low polydispersity indices (PDI). The actual loading of antipsychotic agents into these carriers is driven by a highly synergistic, two-pronged entrapment strategy. First, the core lipophilic aromatic rings of the drug molecule actively seek refuge deep within the primary cyclodextrin cavities, anchoring themselves securely in place through a combination of localized hydrogen bonding and strong hydrophobic interactions. Meanwhile, the more cumbersome, bulky heterocyclic appendages that cannot physically squeeze into these discrete inclusion complexes are instead ensnared within the sprawling interstitial voids of the surrounding crosslinked polymer web. By operating this dual-capture mechanism, the nanosponge matrix can seamlessly accommodate a highly diverse structural payload—securing both strictly lipophilic domains and partially ionized molecular segments simultaneously. Ultimately, this structural versatility is the primary driver behind the exceptionally high encapsulation efficiencies consistently reported for these formulations. For successful nasal administration, the physical dimensions and surface chemistry of these antipsychotic-loaded nanosponges require meticulous optimization.

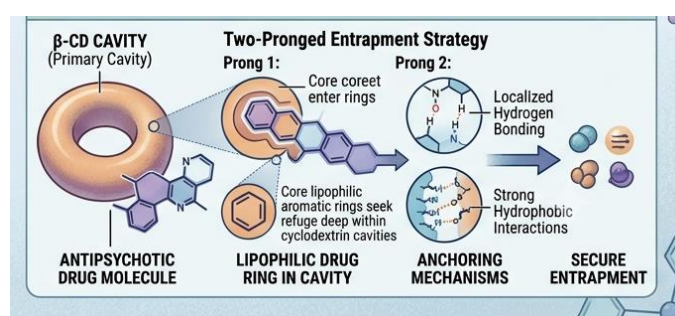


Figure 4 : synergistic drug entrapment mechanism

Formulators strictly constrain the particle diameter to a highly specific window, typically between 100 and 250 nm. This sizing represents a vital biophysical compromise: constructs exceeding the 500 nm threshold are swiftly swept away and eliminated by the nasal cavity's relentless mucociliary clearance apparatus. Conversely, holding the nanoparticle population under 200 nm ensures the carriers remain nimble enough to slip through the dense mucosal meshwork and successfully execute paracellular or perineural transit directly across the olfactory neuroepithelium.

Beyond physical dimensions, surface charge plays a critical role in the formulation's shelf-life and biological safety. These nanocarriers typically display zeta potentials tuned specifically between -15 and -35 mV. This targeted electronegative range generates just enough electrostatic repulsion to keep the colloidal suspension evenly dispersed and prevent unwanted aggregation. More importantly, it achieves this stability while safely avoiding the severe mucosal cytotoxicity frequently associated with highly charged cationic nanoparticles.

Finally, by capitalizing on the dual-loading mechanisms described previously, these matrices boast exceptional drug entrapment efficiencies (EE%). Consistently achieving loading rates anywhere from 68% to well over 90%, this structural capacity

fundamentally solves the innate solubility limits that have historically hindered the delivery of complex, highly hydrophobic antipsychotics.[25]

Table 2 : Characteristics of Antipsychotic-Loaded Nanosponges

Active Pharmaceutical Cargo	Nanosponge Backbone & Linker	Synthetic Route	Hydrodynamic Diameter (nm)	Zeta Potential (mV)	Entrapment Efficiency (EE%)	In Vitro Dissolution Profile
Risperidone	beta-CD, Ethylcellulose, PVA surfactant	Quasi-emulsion solvent diffusion	148.0 – 164.0	-18.4 to -24.2	68.0 – 85.0%	Biphasic: initial burst followed by sustained release over 8 h (>90%)
Aripiprazole	beta-CD, Diphenyl carbonate (DPC, 1:4 ratio)	Solvent condensation in DMF (85 °C)	185.3 ± 14.2	-22.5 ± 1.8	82.4 ± 2.1%	Controlled diffusion-dominated release: 93.85% at 6 h
Haloperidol	beta-CD, Carbonyldiimidazole (CDI)	Emulsification-solvent evaporation	120.5 ± 8.6	-28.4 ± 2.3	78.8 ± 0.8%	Sustained zero-order kinetic release exceeding 12 h
Olanzapine	HP-beta-CD, Pyromellitic dianhydride (PMDA)	Quasi-emulsion solvent diffusion	172.0 ± 11.5	-16.8 ± 1.4	74.2 ± 1.9%	Sustained non-Fickian transport: 85.6% cumulative release at 10 h
Clozapine	beta-CD, Diphenyl carbonate (DPC)	High-pressure homogenization	192 ± 16.0	-21.1 ± 2.0	81.5 ± 2.4%	Prolonged diffusion; avoids initial burst; >80% at 12 h

4.3 Polymer Thermodynamics and In Situ Hydrogel Formulation

While nanosponges excel at solubilizing hydrophobic drugs and shielding them from enzymatic breakdown, simply instilling a basic aqueous suspension into the nose is a fundamentally flawed delivery strategy. The nasal cavity's highly efficient mucociliary clearance apparatus will rapidly sweep these free-floating particles down into the pharynx long before they can permeate the neural mucosa.

To outsmart this aggressive biological defense mechanism, formulators embed the nanocarriers within stimuli-responsive, in situ gelling matrices. These thermosensitive smart-polymers are engineered to behave as highly fluid, low-viscosity liquids while resting at standard room temperature (20 to 25 °C). This initial liquid state is practically vital, as it permits precise, uniform aerosolization through a standard nasal spray pump. However, the moment these droplets make contact with the warmer physiological environment of the nasal cavity (typically ranging from 32 to 35 °C), they undergo a rapid thermodynamic phase shift. Almost instantly, the liquid drops solidify into a robust, semi-solid hydrogel mesh that firmly anchors the nanosponge payload directly against the target epithelium.

To engineer these temperature-responsive matrices, formulation scientists overwhelmingly rely on a specific class of nonionic triblock copolymers built from poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) (PEOx-PPOy-PEOx) architectures. In both academic and industrial settings, these highly versatile macromolecules are universally recognized as poloxamers or pluronics. Within this polymer family, Poloxamer 407 (frequently branded as Pluronic F127) serves as the undisputed workhorse for mucosal delivery systems. Structurally defined by its PEO101-PPO56-PEO101 block arrangement and commanding an average molecular weight of roughly 12,600 Da, it provides the robust biophysical foundation required for the thermogel.

However, to precisely calibrate the phase-transition threshold and mechanical strength of the final hydrogel, formulators rarely use it in isolation. Instead, they routinely blend this primary scaffold with a secondary modulating agent—most notably Poloxamer 188 (Pluronic F68). This noticeably lighter copolymer, characterized by a tighter PEO80-PPO27-PEO80 sequence and a reduced molecular weight of approximately 8,400 Da, acts as a crucial tuning dial, allowing researchers to tightly control the system's thermodynamic behavior and ensure gelation occurs exactly at physiological nasal temperatures.

At a fundamental biophysical level, this rapid sol-to-gel phase shift is entirely driven by micellar thermodynamics. While resting at ambient room temperature—well below the system's critical micelle temperature—the triblock copolymer exists as isolated, free-floating chains known as unimers. In this cold state, both the hydrophilic PEO tails and the hydrophobic PPO cores aggressively hydrogen-bond with the surrounding aqueous solvent, keeping the entire mixture as a highly fluid, easily sprayable liquid.

However, as the formulation is introduced to the warmer nasal cavity (typically climbing toward 30 to 35 °C), the thermodynamic balance abruptly fractures. The influx of thermal energy disrupts and strips away the water molecules previously hydrating the central PPO blocks. Forced into sudden dehydration, these hydrophobic PPO segments instinctively cluster together to minimize water exposure, driving the unimers to spontaneously self-assemble into tightly structured, core-shell micelles. In this new conformation, the dehydrated PPO chains form a dense, shielded inner core, while the still-hydrated PEO tails fan out to create a protective outer corona.

As the localized environment stabilizes at body heat, the volume fraction of these newly formed micelles surges rapidly. Eventually, the spherical structures become so densely packed that they physically interlock, arranging themselves into a highly rigid, ordered cubic liquid-crystalline lattice. Macroscopically, this intricate molecular reorganization manifests as an instantaneous—yet completely reversible—spike in dynamic viscosity. The formulation skyrockets from a watery baseline of under 500 mPa·s to a robust structural peak exceeding 15,000 mPa·s, elegantly transforming a simple liquid spray into a tenacious, semi-solid gel depot right at the anatomical site of absorption.[26]

Relying exclusively on Poloxamer 407 introduces significant mechanical hurdles during product development. When formulators utilize the standard 16–20% w/v concentrations required to achieve a resilient physiological gel, the matrix has a frustrating tendency to solidify well below ambient room temperature (< 22 °C). From a practical standpoint, this premature hardening is disastrous for drug delivery, as the thickening polymer will rapidly jam and clog the narrow mechanisms of standard nasal spray actuators before the patient can even administer a dose.

To rescue the formulation and artificially push the sol-to-gel transition threshold (Tsol-gel) back into the optimal mucosal window of 32 to 35 °C, researchers strategically introduce Poloxamer 188. Because this secondary copolymer is structurally front-loaded with a much higher proportion of hydrophilic PEO blocks relative to its PPO core, it effectively resists early dehydration. Functioning as a precise thermodynamic modifier, it elevates the system's critical micelle temperature, allowing formulation scientists to predictably dial the Tsol-gel upward simply by manipulating the copolymer blending ratios.

Despite their thermodynamic elegance, native poloxamer matrices suffer from a critical functional flaw: they possess inherently weak bioadhesive properties. Left unreinforced, these pure gels are highly susceptible to gradual erosion, slowly washing away under the continuous baseline flow of physiological nasal secretions. To aggressively anchor the formulation and drastically prolong its functional residence time against the target epithelium, researchers fortify the primary matrix with secondary mucoadhesive polymers.

Formulators typically rely on two distinct classes of bioadhesive agents to achieve this structural reinforcement:

Cellulosic Interpenetration: Incorporating heavy-duty cellulosic derivatives—specifically sodium carboxymethylcellulose (Na-CMC) or specialized high-viscosity grades of hydroxypropyl methylcellulose (such as HPMC K4M, K15M, or K100M)—allows these secondary, long-chain polymers to physically interpenetrate the foundational poloxamer mesh. This physical entanglement deeply reinforces the architectural integrity of the gel depot through an extensive, stabilizing network of supplementary hydrogen bonds.

Polyacrylate Anchoring: Alternatively, high-molecular-weight polyacrylates like Carbopol 934, Carbopol 940, or Carbopol 974P act as aggressive chemical anchors. They secure the matrix directly to the biological tissue by driving their abundant carboxyl groups to form tenacious hydrogen bonds with the oligosaccharide chains protruding from the host's native mucin glycoproteins. However, formulation scientists must tread carefully when deploying these polyacrylate resins. Carbopol concentrations are strictly capped below a 0.5% w/v threshold. Exceeding this limit not only risks inducing severe localized irritation along the sensitive nasal mucosa but also artificially depresses the system's sol-to-gel transition temperature well below the required physiological target window.

Beyond the cellulosic and polyacrylate options, formulators frequently turn to chitosan to fundamentally alter the system's bioadhesive mechanics. As a naturally derived polycationic polysaccharide harvested from chitin, chitosan abandons standard hydrogen bonding in favor of aggressive electrostatic attraction. Once introduced to the nasal environment, its abundant primary amine groups become heavily protonated ($-NH_3^+$). These dense, localized positive charges actively seek out and lock onto the negatively charged sialic acid and sulfate residues that heavily coat native mucosal glycoproteins, creating a profound electrochemical anchor between the polymer gel and the biological tissue.

More importantly, chitosan operates as a dynamic permeation enhancer rather than just a static bioadhesive structural component. It possesses the unique biological capability to temporarily compromise the epithelial barrier itself. By actively forcing the redistribution of critical tight junction structural proteins—specifically claudin-4 and occludin—chitosan effectively unlocks the rigid intercellular seals. This transient structural shift pries open a highly efficient paracellular corridor, allowing the therapeutic nanoparticles to bypass cellular membranes entirely and wash directly across the epithelial layer toward the central nervous system. From a strictly rheological perspective, these in situ matrices must exhibit pronounced pseudoplastic, shear-thinning behavior to function effectively in a real-world clinical setting. The physical mechanics of administration are highly dynamic. As the formulation is aggressively forced through the narrow nozzle of a standard nasal actuator—subjecting the fluid to extreme, localized shear rates that frequently exceed $\gamma > 1000s^{-1}$ —the heavily intertwined polymer chains are temporarily stretched and pulled apart. This sudden, shear-induced unspooling causes an immediate collapse in the fluid's structural viscosity, allowing what is normally a thick suspension to be cleanly atomized into a fine, uniform aerosol cloud.

However, this mechanical thinning is completely transient. The precise moment those micro-droplets strike the stationary mucosal surface, the applied shear stress drops to zero. Freed from that mechanical distortion, the polymer networks instantly recoil and re-entangle, immediately recovering their baseline high viscosity to prevent the liquid from dripping down the pharynx. When this rapid rheological bounce-back is simultaneously exposed to the physiological warmth of the nasal epithelium, the entire matrix is driven through its thermodynamic sol-to-gel transition, ultimately locking the delivery system into a rigid depot in a remarkably brief 10 to 30 seconds.

Table 3 : Rheological and Mechanical Properties of Thermogels

Base Polymer System	Mucoadhesive Agent & Concentration	Gelation Temp (Tsol-gel °C)	Gelation Time (s)	Mucoadhesive Strength (dyn/cm ²)	Dynamic Viscosity (Sol 25°C vs Gelat 35°C, mPa·s)	Physical Stability & Mechanical Characteristics
Poloxamer 407 (18.0%)	HPMC K100M (0.4% w/v)	34.25 ± 1.10	12.35 ± 1.4	1365 ± 48	410 ± 25 vs 14,890 ± 450	High mechanical strength; stable over 3 months accelerated testing
Poloxamer 407 (16.0%) / P188 (1.5%)	Carbopol 940 (0.2% w/v)	33.40 ± 0.80	18.50 ± 2.1	1650 ± 72	350 ± 18 vs 16,200 ± 520	Resists ciliary wash-out; sustained drug release kinetics
Poloxamer 407 (17.5%)	Chitosan (0.5% w/v)	32.80 ± 0.50	15.20 ± 1.8	2150 ± 95	520 ± 30 vs 18,450 ± 610	Enhances permeation via transient tight-junction opening
Pluronic 188 (56.25%)	Sodium CMC (0.5% w/v)	35.00 ± 0.02	24.00 ± 3.0	1120 ± 40	329 ± 15 vs 15,667 ± 410	Rapid thermal response; stable pseudoplastic shear profile
Deacetylated Gellan Gum (0.6%)	Carbopol 934 (0.15% w/v)	Ion-activated (34.0°C)	< 60.0	1450 ± 55	380 ± 22 vs 13,500 ± 380	Dual-responsive matrix activated by ions and temperature

4.4 In Vitro, Ex Vivo, and Preclinical In Vivo Performance

To rigorously validate the clinical viability of these nanosponge-infused thermogels, researchers cannot rely on a single experimental endpoint. Instead, the formulation must survive a strict, multi-tiered analytical pipeline. This testing cascade follows a highly deliberate evolutionary trajectory: it begins at the benchtop by mapping foundational *in vitro* release kinetics, scales up to quantify *ex vivo* permeation across explanted mucosal tissues, and ultimately culminates in complex *in vivo* neuro-pharmacokinetic profiling and behavioral efficacy trials within living biological models.

When mapping exactly how these hydrophobic antipsychotics escape the formulation, pharmacokineticists characterize the release profile as a strict, dual-barrier mass transport process.

The therapeutic payload cannot simply wash away. First, individual drug molecules must physically uncouple and dissociate from their secure binding sites deep within the cyclodextrin cavities or the interstitial voids of the nanosponge matrix. Only after breaking free from this primary chemical anchor can the molecules initiate the second phase of their journey: slowly navigating and diffusing across the dense, crosslinked aqueous mesh of the surrounding hydrogel depot.

The functional advantage of this nested architecture becomes undeniably clear when evaluated under physiologically accurate parameters—specifically utilizing simulated nasal fluid (SNF) tightly calibrated to a pH of 6.4 ± 0.1 and a mucosal temperature of 34 °C. While basic, unencapsulated nanosuspensions notoriously dump their cargo almost immediately upon contact with the mucosa, this highly engineered composite matrix successfully suppresses that initial burst release. By bottlenecking the drug flow through two distinct physical barriers, the system guarantees a highly controlled, sustained delivery profile.

Looking specifically at risperidone, when formulators embed these nanosponges within a foundational Poloxamer 407 and HPMC gel matrix, the system effectively throttles the initial dose dump. The architecture permits a strictly controlled initial effusion of just 15% to 20% during the primary hour, seamlessly transitioning into a sustained delivery phase that ultimately yields a near-total 98.18% release at the 8-hour mark.

The biophysical advantage of this approach becomes even more stark when evaluating aripiprazole platforms. Due to the molecule's notoriously poor aqueous solubility, raw, unformulated drug suspensions tragically stall, releasing a clinically inadequate $41.92 \pm 0.36\%$ of their payload. In sharp contrast, the engineered nanosponge *in situ* gels completely bypass this solubility bottleneck, successfully driving cumulative release to an impressive $93.85 \pm 0.43\%$ over a tight 6-hour window.

To mathematically characterize these kinetic release trajectories, pharmacokineticists routinely map the empirical dissolution data directly against the Korsmeyer-Peppas power law model:

$$\frac{M_t}{M_\infty} = K_{KP} \cdot t^n$$

Within this framework, the fractional drug release (M_t/M_∞) is governed by the system's inherent kinetic rate constant (K_{KP}) alongside the critical diffusional exponent (n).

It is this specific n exponent that reveals the actual biophysical mechanics operating inside the matrix. Across these nanosponge-infused thermogels, formulation scientists consistently derive n values landing squarely in the window between 0.5 and 0.85. In polymeric thermodynamics, this specific range conclusively dictates an anomalous, non-Fickian transport mechanism. Ultimately, this proves that the therapeutic cargo isn't just passively leaching out of the system; instead, the release is a highly complex, dual-

driven physical event. It relies simultaneously on the drug navigating through the restrictive nanosponge pores *and* the macroscopic swelling and structural relaxation of the surrounding hydrogel web.

To validate these formulations beyond mathematical dissolution models, investigators rely on rigorous *ex vivo* permeation assays, typically mounting excised porcine, bovine, or ovine nasal mucosa within precisely calibrated Franz diffusion cell architectures. Data extracted from these isolated biological interfaces conclusively demonstrate that embedding the nanocarriers within the thermogel matrix aggressively drives up both the steady-state flux (J_{ss}) and the overall apparent permeability coefficient (K_p) of the therapeutic cargo.

The biophysical secret to this enhanced transmucosal penetration lies directly in the chemical behavior of the hyper-crosslinked cyclodextrins. Operating as highly efficient permeation modulators, these rigid macrocycles actively leach and extract cholesterol and sphingolipids straight out of the phospholipid bilayers of the surrounding epithelial cells. This highly localized lipid depletion triggers a transient collapse in innate barrier resistance, safely prying open the mucosal gateway without inducing any permanent necrotic or cytotoxic tissue damage.

Working in perfect synergy with this cellular-level disruption, the overarching bioadhesive hydrogel physically halts the innate, continuous drainage of local mucosal fluids. By stubbornly anchoring the delivery system in place, the gel depot ensures that an overwhelming, localized concentration gradient is sustained continuously right at the apical membrane of the neuroepithelium—practically forcing the drug across the biological divide.[27]

When transitioning these engineered platforms into living biological systems, rigorous preclinical pharmacokinetic models conclusively validate their superior neuro-targeting capabilities. Using male Wistar albino rats as the primary *in vivo* baseline, investigators directly benchmarked an intranasal risperidone nanosponge thermogel (specifically the MR5 formulation, anchored by a Poloxamer 407 and HPMC matrix) against traditional oral and intravenous controls.

The neuro-pharmacokinetic advantage of this localized delivery architecture is immediately striking. By anchoring the drug directly at the olfactory and trigeminal interfaces, the *insitu* gel drove overall brain exposure—quantified by the area under the concentration-time curve ($AUC_{0-\infty}$)—to an impressive 5.4-fold increase over an equivalent oral solution ($p < 0.05$). Following mucosal administration, researchers recorded a robust peak brain concentration (C_{max}) of 3.49 $\mu\text{g/mL}$ firmly established at a T_{max} of just 2 hours.

More critically, the hydrogel depot fundamentally rewrites the formulation's elimination kinetics. Standard intravenous delivery is notoriously plagued by aggressive, immediate plasma spikes followed by rapid systemic clearance. In stark contrast, the mucoadhesive nanosponge matrix effectively drip-feeds the neuroepithelium, radically extending the terminal elimination half-life ($t_{1/2}$) out to roughly 39 to 41 hours, alongside an equally protracted mean residence time (MRT) of 58 to 60 hours. This structural persistence guarantees an uninterrupted, sustained neurological exposure completely decoupled from volatile systemic blood concentrations.

This neuro-pharmacokinetic dominance is equally pronounced when evaluating aripiprazole platforms. By embedding an engineered ARP-NS construct (a β -CD/DPC nanosponge dispersed securely within a dual Carbopol 940 and HPMC K100 matrix), formulators successfully drove immense drug concentrations directly into the cerebral tissue. The formulation established a formidable brain peak concentration (C_{max}) of 4929 ± 21.56 ng/mL precisely at the 3-hour mark, securing an aggregate brain AUC of 930.35 ± 24.5 ng $\cdot$ h/mL.

Beyond raw mathematical metrics, this optimized delivery profile translates directly into measurable clinical efficacy. When tested against psychosis-induced rodent models, the *insitu* gel triggered a profound, prolonged suppression of apomorphine-induced hyperlocomotion. Crucially, it not only vastly outperformed equivalent oral aripiprazole solutions, but the localized delivery mechanism also successfully shielded the subjects from the severe motor deficits typically associated with systemic dose dumping. To definitively prove that these formulations are actually exploiting neural corridors rather than simply leaching into the bloodstream and crossing the blood-brain barrier conventionally, pharmacokineticists map specific brain-targeting indices. Evaluations of intranasal haloperidol nanocarriers illustrate this mechanism perfectly. The formulation yielded an exceptional Drug Targeting Efficiency (DTE%) of 597.57% alongside a Direct Transport Percentage (DTP%) of 83.27%. Translating these kinetic metrics into biological reality confirms a massive architectural victory for the delivery system: well over 83% of the haloperidol successfully entering the central nervous system bypassed systemic vascular redistribution entirely, riding the direct olfactory and trigeminal nerve tracks straight into the brain.

Table 4 : Preclinical Efficacy of Intranasal Antipsychotic Nanosponges

Antipsychotic Formulation	Polymer & Gelling Vehicle	Preclinical Model	Brain Cmax & Tmax	Brain Exposure (AUC0-t) Relative to Control	Drug Targeting Efficiency (DTE%)	Direct Transport Percentage (DTP%)	Behavioral & Pharmacodynamic Findings
Risperidone Nanosponge In Situ Gel	Poloxamer 407, HPMC K100M	Male Wistar albino rats	3.49 $\mu\text{g/mL}$ at 2.0 h	~5.4-fold higher vs oral solution	264.5%	76.8%	Sustained CNS availability; prolonged half-life

							($t_{1/2} \approx 40$ h); reduced EPS
Aripiprazole Nanosponge In Situ Gel	Carbopol 940, HPMC K100	Male Sprague-Dawley rats	4929 ng/mL at 3.0 h	AUC = 930.35 ng.h/mL vs oral	312.0%	84.2%	Suppressed apomorphine-induced hyperactivity in psychotic rats
Haloperidol Nanoparticulate Gel	Poloxamer 407, PVA, Cubosomes	Wistar rats	1850 ng/g at 1.5 h	4.2-fold increase vs IV solution	597.57%	83.27%	Reversal of amphetamine hyperlocomotion; reduced catalepsy
Ziprasidone Lipid-Polymer Hybrid Gel	Chitosan, Poloxamer 407	Albino Wistar rats	2840 ng/mL at 1.0 h	3.9-fold increase vs IV solution	390.0%	74.68%	Normalized schizophrenic hypermobility; reduced QT prolongation liability
Quetiapine Fumarate Niosomal Gel	Chitosan, Poloxamer 407 / P188	Sprague-Dawley rats	1420 ng/mL at 2.0 h	3.6-fold higher vs oral suspension	285.4%	68.9%	Sustained sedation and antipsychotic action; bypassed hepatic first-pass

4.5 Translational Considerations, Safety, and Clinical Outlook

Pushing these nanosponge infused matrices beyond the isolated preclinical phase and into real-world clinical deployment hinges on resolving three formidable translational bottlenecks. Formulation scientists must now definitively prove absolute, long-term mucosal biocompatibility, successfully scale up these complex thermodynamic blends for industrial-level manufacturing, and guarantee flawless mechanical integration with commercial nasal spray actuators.

To ensure patient safety and long-term compliance, formulators must fundamentally respect the fragile biological architecture of the nasal cavity. The local epithelial lining is heavily populated by pseudostratified columnar cells, whose cilia must maintain a relentless mechanical rhythm of 10 to 15 Hz to drive innate mucociliary clearance. If a therapeutic matrix paralyzes this ciliary beat or chemically degrades the mucosal surface, it immediately compromises the patient's immune barrier, severely elevating the risk of chronic rhinosinusitis and opportunistic respiratory infections.

To definitively prove mucosal compatibility, researchers subject these formulations to strict *ex vivo* ciliotoxicity assays. Utilizing freshly excised ovine or porcine nasal mucosa, the biological tissues are exposed to the thermogels for prolonged 1- to 4-hour evaluation windows. When strictly benchmarked against the catastrophic tissue destruction of a 100% isopropyl alcohol positive control and the benign physiological baseline of phosphate-buffered saline (pH 6.4), the engineered nanosponge matrices perform flawlessly.

High-resolution histopathological screening, visualized through standard hematoxylin and eosin (H&E) staining, confirms that the optimized β -CD, Poloxamer 407, and HPMC platforms leave the epithelial topography completely undisturbed. Post-exposure, the basement membrane remains structurally rigid, the ciliary borders show absolutely zero signs of blunting or necrosis, and the underlying submucosal architecture escapes without any inflammatory damage.

This exceptional safety profile is not accidental; it is the direct biophysical consequence of meticulous excipient selection. The formulation's primary structural components—from the naturally derived, non-toxic cyclodextrin oligosaccharides to the highly inert, non-ionic poloxamer scaffolds—are inherently biocompatible. More importantly, by securely locking the aggressive antipsychotic molecules inside the nanosponge cavities, the system completely prevents localized drug precipitation and physical crystallization, effectively shielding the delicate mucosa from chemical burns.

Scaling these complex architectures from the laboratory bench to commercial manufacturing floors introduces severe, highly specific sterilization hurdles. Conventional terminal sterilization protocols are fundamentally too destructive for these thermo-responsive composites. Subjecting the loaded formulation to standard steam autoclaving (121 °C at 15 psi) rapidly degrades the delicate crosslinked cyclodextrin networks and instantly triggers aggressive thermal auto-oxidation across the poloxamer chains. Similarly, deploying gamma irradiation risks fracturing the polymer framework entirely through random chain scission, radically altering the precise molecular weights required for accurate physiological gelation.

To successfully circumvent these structural failures, industrial process engineers must pivot strictly to advanced aseptic compounding. The manufacturing workflow is strictly compartmentalized: the primary cyclodextrin nanosponges are independently synthesized, rigorously purified, and sterilized using either validated ethylene oxide gas exposure or absolute sterile filtration. Only after this isolated preparation is the sterile nanoparticulate powder gently folded into a pre-filtered poloxamer vehicle that has been exclusively cold-sterilized to preserve its thermodynamic integrity.

Once assembled, the long-term physical stability of the finished product dictates strict cold-chain logistics. Over prolonged periods, these dense polymeric systems are highly susceptible to creeping phase separation and gradual particle sedimentation. To actively suspend this physical degradation, commercial batches must be rigidly confined to refrigerated storage (2 to 8 °C). This continuous chilling protocol locks the matrix in a highly stable, completely unaggregated liquid sol state, ensuring it remains flawlessly primed for immediate, room-temperature aerosolization the moment it reaches the patient's hands.

Finally, the chemical legacy of the original synthesis demands intense analytical scrutiny. Building nanosponges requires aggressive crosslinking agents, which inherently leave behind dangerous molecular debris—most notably, toxic free phenol cleaved from diphenyl carbonate (DPC) or unreacted imidazole residues stemming from carbonyldiimidazole (CDI) reactions. To aggressively strip these hazards from the final product, the raw matrices undergo relentless Soxhlet extraction followed by deep lyophilization. Before any batch clears quality assurance, these intensive purification sweeps must be analytically validated through high-resolution

chromatography, guaranteeing that all trace impurities sit securely below the rigorous residual solvent limits mandated by global ICH Q3C guidelines.

Translating these thermodynamic marvels into measurable clinical efficacy ultimately hinges on mechanical precision: the formulation must physically reach the remote olfactory neuroepithelium tucked high within the superior nasal vault.

Relying on conventional, off-the-shelf nasal spray actuators practically guarantees failure. These crude pumps aggressively dump the vast majority of their payload straight into the anterior, non-ciliated nasal vestibule. From there, the droplets either drain back out of the nostril as anterior run-off or are swiftly swept down the respiratory tract and swallowed into the pharynx, missing the neural target entirely.

To rescue the anatomical delivery, clinical engineers are increasingly turning to highly specialized, bidirectional breath-powered devices. By actively harnessing the aerodynamic force of the patient's own exhalation, these advanced actuators mechanically force the soft palate to snap shut. This critical reflex perfectly seals off the deep respiratory tract, creating a closed aerodynamic circuit that powerfully lofts the aerosol plume directly upward into the difficult-to-reach superior olfactory cleft.

Beyond the gross aerodynamics, the device's nozzle must flawlessly shear the polymer fluid into a strictly controlled droplet size distribution, constrained tightly between 10 and 50 micrometers. This sizing is an absolute biophysical necessity. Atomizing the fluid below the 10-micrometer threshold creates a dangerous, inhalable mist that risks bypassing the nasal cavity entirely and lodging deep within the pulmonary bed. Conversely, generating heavy, sluggish droplets that exceed 50 micrometers inevitably triggers immediate anterior run-off before the polymer has time to solidify.

Fortunately, the baseline thermodynamics of the formulation perfectly support this precise mechanical atomization. Because the matrix rests as a highly fluid, low-viscosity liquid at ambient room temperatures (20 to 25 °C), it effortlessly passes through these narrow-orifice nozzles without demanding excessive, hand-fatiguing actuation force from the patient. The exact moment this finely milled aerosol cloud strikes the warm olfactory mucosa (32 to 35 °C), the system initiates its rapid sol-to-gel transition. This rapid hardening permanently anchors the delivery depot precisely over the neural gateway, aggressively resisting mucociliary wash-out and guaranteeing a sustained, direct chemical corridor straight into the central nervous system.

5. Conclusion

Nanosponge-infused, thermoreversible hydrogels represent a paradigm shift in neurotherapeutics, successfully overcoming the profound physiological and pharmacokinetic hurdles that have historically crippled conventional antipsychotic delivery. By anchoring hydrophobic neuroactive cargo within crosslinked cyclodextrin networks, these advanced systems permanently conquer innate aqueous insolubility, shield fragile molecules from rapid enzymatic breakdown, and tightly throttle release kinetics.

When these nanocarriers are embedded within a poloxamer and mucoadhesive matrix, the resulting formulation behaves as an agile, low-viscosity liquid during room-temperature aerosolization, only to undergo an instantaneous thermal phase transition upon contacting the warm nasal mucosa (32 to 35 °C). This rapid thermodynamic locking completely outwits the relentless mechanical drag of mucociliary clearance, anchoring a persistent drug depot directly against the target tissue. Preclinical evaluations confirm the extraordinary clinical dividends of this architecture: living animal models demonstrate massive direct brain-targeting efficiencies exceeding DTE > 200% alongside dominant direct transport percentages of DTP > 70%.

By aggressively bypassing hepatic first-pass metabolism and shielding systemic circulation, this localized delivery vector succeeds where traditional oral and intravenous routes fail—delivering towering cerebral concentrations while actively mitigating debilitating extrapyramidal symptoms and cardiometabolic liabilities. Translating this transformative platform from benchtop promise to psychiatric practice now requires a disciplined final push: scaling robust aseptic manufacturing pipelines, locking down long-term physical stability under cold-chain logistics, and validating precise mucosal deposition in human clinical trials via targeted bidirectional delivery devices.

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