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REVIEW

Stimuli-Responsive Nasal in situ Gel Drug Delivery Systems: from Material Design to Clinical Translation

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Abstract: As a novel drug delivery system responsive to environmental stimuli (temperature, pH, ionic strength, etc). nasal in situ gels undergo phase transition to provide breakthrough solutions for precision and long-term management of nasal disorders through the integration of targeted therapy and sustained-release technology. Following nasal administration, the liquid formulation rapidly transforms into a semi-solid gel depot on the mucosal surface, significantly prolonging drug residence time and reducing drug loss due to mucociliary clearance. This process enhances local drug concentration and therapeutic persistence. Incorporating mucoadhesive technology and controlled-release drug-loading systems, this platform enables precise delivery of anti-inflammatory, antihistaminic, and immunomodulatory agents to lesion sites. It effectively mitigates systemic side effects (e.g. drowsiness, hepatic/renal burden) associated with conventional dosage forms while reinforcing nasal mucosal barrier repair. Clinical studies confirm its superior efficacy and safety profile in conditions requiring long-term therapy, including allergic rhinitis, sinusitis, and central nervous system disorders. Its mild gelation properties enhance patient tolerance, and single/every-other-day dosing regimens significantly improve compliance. Further optimization of release kinetics through multi-level drug-loading techniques (e.g. composite nanoparticles) demonstrates potential in gene therapy and vaccine delivery. This review systematically examines material design strategies, drug release mechanisms, clinical advancements, and translational challenges, with focused analysis on the impact of gelation kinetics on delivery efficiency, bottlenecks in scaled-up production. The work aims to provide theoretical foundations for optimized design and clinical translation while exploring future prospects for multifaceted applications in the era of precision medicine.

Keywords: nasal drug delivery, in situ gel, drug delivery system, sustained-release technology, clinical translation

Introduction

The nasal cavity, serving as a critical gateway to the human respiratory tract, functions not only as an organ for respiration and olfaction but also represents a potential target for drug delivery.[1] Nasal drug delivery systems have gained attention for their non-invasiveness and high mucosal permeability.[2,3] However, conventional nasal sprays and drops are limited by ciliary clearance, mucus barrier, rapid elimination, and low bioavailability, which impede sustained drug retention.[4] To address these challenges, nasal in situ gels (NISG) have been developed as smart-responsive systems that undergo liquid-to-gel phase transition, offering a novel approach for precision management of nasal disorders.[1,5]

The nasal mucosa possesses high absorption potential.[6] Sustained ciliary beating at 5–6 mm/min restricts intranasal residence time typically to <20 minutes, significantly narrowing the therapeutic window for local treatment.[7] Mucus glycoproteins and enzymes may degrade drugs, and tight junctions limit macromolecule permeation.[8] Compounded by the limited nasal cavity capacity (~0.2 mL per nostril), excessive administration risks drug loss via the nasolacrimal duct or unintended systemic absorption.[9] Conventional solution-based sprays exhibit dose dumping and fail to maintain therapeutic concentrations, requiring frequent dosing (3–4 times daily) and reducing compliance.[10] To address these limitations,

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developing novel delivery systems integrating prolonged retention, controlled release, and mucoadhesive properties has become a research priority. NISG represent a paradigmatic breakthrough in this field.

NISG use environmentally responsive polymers that trigger phase transition upon exposure to nasal temperature, pH, or ions.[11] Gelation occurs within seconds to minutes, forming a drug depot that adheres to the mucosa and extends release to hours or days.[12] Compared to conventional dosage forms, this technology demonstrates multifaceted advantages: 1) Precision gelation and controlled release: Through combinatorial design of thermosensitive (eg., poloxamers, chitosan derivatives), pH-sensitive (eg., carbomers), or ion-triggered (eg., sodium alginate) materials, the system achieves targeted gelation within the nasal cavity. Subsequent drug release follows zero- or first-order kinetics via diffusion, erosion, or ion-exchange mechanisms, maintaining stable local drug concentrations.[13,14] 2) Reduced systemic exposure: Enhanced local retention minimizes drug absorption into systemic circulation through nasomucosal capillaries, thereby mitigating systemic side effects (eg., adrenal suppression risk with corticosteroids). 3) Biofunctional matrices: Certain gel substrates (eg., hyaluronic acid, chitosan) exhibit inherent bioactivities including moisturization, anti-inflammation, or epithelial repair promotion, synergistically improving the nasal microenvironment with therapeutic agents.[15] 4) Enhanced tolerability: The gentle gelation process eliminates nasal irritation associated with traditional powder inhalers, while single-daily dosing improves patient comfort and compliance.

While several previous reviews have discussed the broader field of intranasal drug delivery or individual aspects of in situ gel systems, the present review aims to provide a more integrated perspective on stimuli-responsive nasal in situ gels. Specifically, this review brings together material design, stimuli-triggered gelation kinetics, therapeutic applications, and translational challenges within a single analytical framework. In addition to summarizing representative formulation strategies, we emphasize how phase-transition behavior under nasal physiological conditions influences delivery efficiency and therapeutic performance. We also highlight practical barriers to clinical translation, including sterilization compatibility, physicochemical stability, and scale-up manufacturing, which are often less thoroughly discussed in earlier reviews.

Currently, NISG have demonstrated significant therapeutic potential across multiple nasal pathologies. In allergic rhinitis (affecting 10–30% of the global population), in situ gels enable sustained release of antihistamines or corticosteroids,[16] reducing dosing frequency and minimizing oropharyngeal deposition.[17,18] For chronic rhinosinusitis with nasal polyps, they deliver antibiotics or immunomodulators to delay disease recurrence.[19] Postoperatively, gel systems serve as hemostatic materials or anti-adhesion barriers.[20,21] Notably, studies confirm that incorporating secondary drug-loading platforms – such as composite nanoparticles, liposomes, or porous microspheres – enhances loading efficiency for hydrophobic drugs (eg., tacrolimus) and enables coordinated multi-drug release (eg., anti-inflammatories + antimicrobials). This approach provides viable strategies for combinatorial therapy in complex pathological contexts.[22] Despite promising preclinical results, NISG face clinical translation challenges: narrow gelation windows of thermosensitive materials,[1] stability issues during storage,[23] potential ciliary toxicity with repeated use,[22] and variability due to different nasal pathologies.[24]

Looking ahead, the convergence of materials science, nanotechnology, and artificial intelligence promises transformative advancements in nasal in situ gels. Key developmental trajectories include: 1) Multi-stimuli-responsive gel systems (eg., temperature + pH + enzyme-sensitive) enabling precise lesion targeting and on-demand drug release.[25] 2) Therapeutic expansion into nasal vaccines (eg., influenza), gene therapy (eg., siRNA delivery), and neurodegenerative disease interventions via nose-to-brain pathways (eg., Alzheimer's disease).[26] 3) Intelligent delivery platforms incorporating smart nebulization devices with integrated dose-monitoring sensors for real-time feedback and individualized regimen adaptation.[27] Figure 1 provides a schematic overview of the multi-scale working principles of stimuli-responsive nasal in situ gel systems. The left panel illustrates the macro-level delivery pathways following intranasal administration, showing how drugs can bypass the blood-brain barrier (BBB) via the olfactory and trigeminal nerves to target central nervous system disorders (eg., Alzheimer's disease, Parkinson's disease, depression), while also directly reaching localized nasal diseases (eg., rhinitis, sinusitis, nasal polyps). The right panel depicts the micro-level mechanisms, including stimuli-responsive sol-to-gel phase transition, formation of a gel network embedded with nanocomposites (liposomes, nanoparticles), and the resulting enhancement of mucoadhesion and resistance to mucociliary clearance. Together, this figure integrates the anatomical, pathophysiological, and formulation design aspects discussed throughout this review.

This comprehensive review employed literature retrieval through PubMed and Web of Science databases. Search strategies incorporated keyword combinations (eg., "gel" OR " hydrogel" OR "nasal" with synonymous terms) using Boolean operators

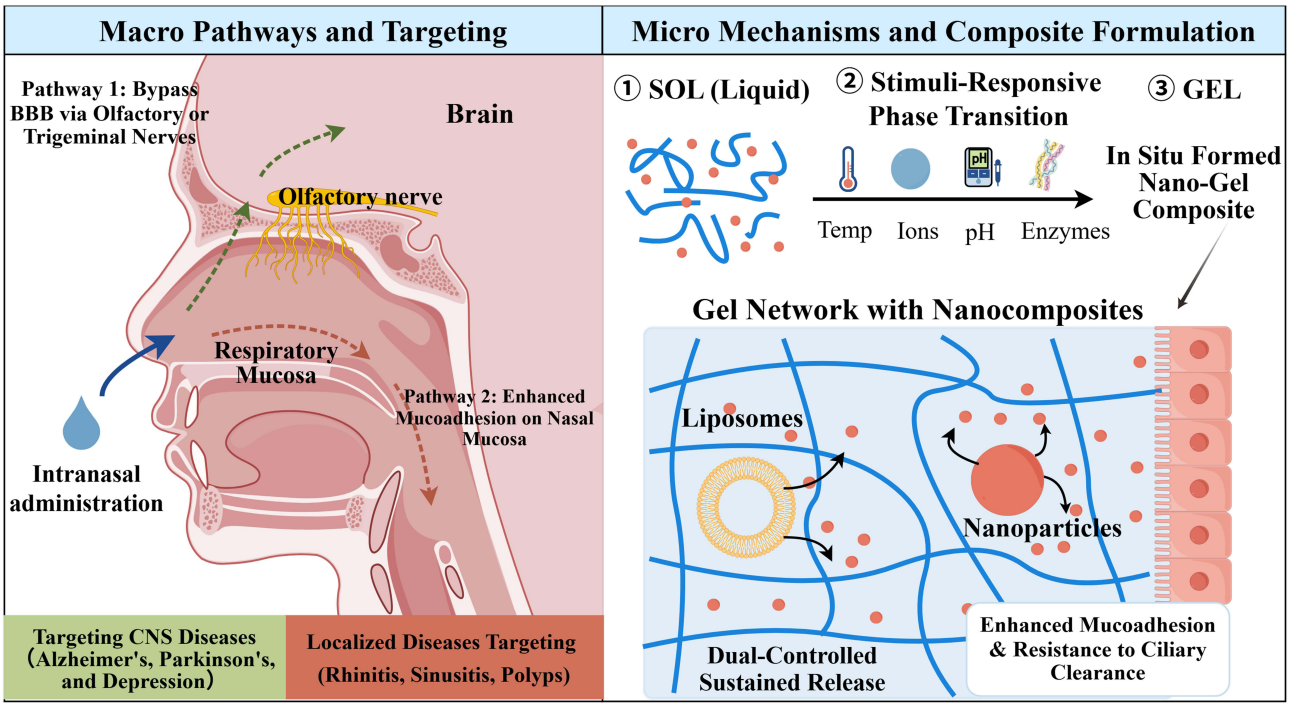

Figure 1 Schematic illustration of stimuli-responsive nasal in situ gel drug delivery systems. Left panel (Macro pathways and targeting): Intranasal administration enables drug delivery via olfactory and trigeminal nerves to bypass the blood-brain barrier (BBB) for central nervous system diseases (Alzheimer's, Parkinson's, depression), as well as direct targeting of localized nasal diseases (rhinitis, sinusitis, nasal polyps). Right panel (Micro mechanisms and composite formulation): The system undergoes stimuli-responsive sol-to-gel phase transition, forming a gel network embedded with nanocomposites (liposomes, nanoparticles). This architecture enhances mucoadhesion and resistance to mucociliary clearance, enabling sustained drug release.

(AND/OR). Inclusion criteria encompassed: English-language original research, reviews, and clinical trials explicitly addressing gel application mechanisms in nasal contexts. Non-relevant studies and non-English publications were excluded. A three-tier screening process-initial title/abstract assessment, full-text evaluation, and data extraction-ensured topical relevance. This review critically examines material design strategies for NISG, drug release mechanisms, clinical application advancements and translational medicine challenges. With particular emphasis on: How gelation kinetics under different stimuli-responsive mechanisms influence drug delivery efficiency? How Clinical validation of therapeutic advantages and safety profiles in existing studies? What Critical technological bottlenecks requiring resolution from laboratory to industrialization? By integrating recent fundamental research and clinical trial data, this review aims to provide theoretical references for optimizing NISG design and clinical translation, while projecting their multidimensional application scenarios in the era of precision medicine.

Material Design Strategies and Gelation Kinetics

The functional foundation of NISG lies in their material design, where distinct stimuli-responsive mechanisms govern gelation kinetics-critically determining drug delivery efficiency. Current predominant design strategies encompass four categories: thermosensitive, ion-sensitive, pH-sensitive, and enzyme/biomolecule-responsive systems, each exhibiting distinctive gelation mechanisms and application profiles (Table 1).

Thermosensitive Gels

Thermosensitive gels represent the most extensively studied category of NISG systems, with poloxamer 407 (P407) and its composite formulations with poloxamer 188 (P188) being predominant.[30] These polymers exhibit reverse thermal gelation behavior-existing as free-flowing solutions at ambient temperature but rapidly forming three-dimensional network structures at physiological temperatures (~33–34°C).[15] The gelation mechanism primarily relies on intermolecular hydrophobic

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Table 1 Comparative Analysis of Four Types of Stimuli-Responsive Nasal in situ Gels

Property	Thermosensitive	Ion-Sensitive	pH-Sensitive	Enzyme/Biomolecule-Responsive
Representative materials	Poloxamer 407; Poloxamer 188	Gellan gum; Deacetylated Gellan gum	Carbomer, Chitosan	Hyaluronic acid; Enzyme-substrate peptides
Gelation trigger	Temperature increase (25°C→33–34°C)	Cations (Na^+, K^+, Ca^{2+})	pH variation (4.0→5.5–6.5)	Specific enzymes/biomolecules
Gelation time	30–60 s	5–20 s	20–40 s	Seconds to minutes
Key modulation parameters	Polymer concentration, P407/P188 ratio	Gellan gum concentration; Ionic strength	pH value; Ionic strength	Enzyme concentration/activity; Local biomolecule expression levels
Primary advantages	Well-defined thermoresponsiveness; Tunable properties	Rapid response; Strong mucoadhesion	High biocompatibility; Biodegradability	High biocompatibility; Targeted response to pathological microenvironments
Limitations	Potential tissue irritation at high concentrations	Gel strength significantly influenced by ionic concentration	Inter-individual nasal pH variations may affect performance	Dependency on specific enzyme expression levels; Gelation failure under insufficient enzyme activity
Typical applications	Antidepressants (eg., Mirtazapine); Neuroprotective agents[28]	Antibiotics (eg., Ceftriaxone);[28] Amoxicillin[29]	Anti-inflammatory drugs; Topical therapeutics[1]	Postoperative hemostasis; Anti-inflammatory therapy[5]

interactions: as temperature increases, polypropylene oxide (PPO) segments in P407 undergo dehydration and entanglement, forming hydrophobic domains that establish gel networks.[11]

Critical gelation kinetic parameters encompass the sol-gel transition temperature and gelation time. Research demonstrates an inverse correlation between P407 concentration and transition temperature-increasing concentration from 18% to 25% reduces this temperature from 30°C to 24°C.[31] Conversely, incorporating P188 elevates the transition temperature moderately while enhancing formulation fluidity.[32] Precise control of gelation time is paramount for delivery efficiency: durations <10 seconds risk administration challenges, whereas >60 seconds increase susceptibility to precocious clearance by nasal cilia.[1] The donepezil hydrochloride thermosensitive in situ gel achieved an optimal equilibrium (32°C transition, 40-second gelation) through calibrated P407/carbomer 188 ratios. This resulted in enhanced bioavailability and superior cerebral distribution, thereby significantly improving drug brain-targeting efficiency.[33]

Rheological investigations demonstrate that thermosensitive gels undergo abrupt transitions in viscoelastic moduli (G'/G") at the phase transition point. Below the gelation temperature, the viscous modulus (G") predominates, conferring viscous liquid characteristics to the system. Upon reaching the gelation temperature, the elastic modulus (G') rapidly exceeds G", effecting transformation into an elastic gel.[34] This rheological shift directly governs drug release kinetics—the elastic gel network effectively retards drug diffusion, achieving sustained release. In vitro release studies of ibuprofen-loaded thermosensitive gel corroborate this mechanism, demonstrating only 92% cumulative drug release over 8 h, significantly lower than the rapid release profile of solution formulations.[35]

Ion-Sensitive Gels

Representative matrices for ion-sensitive gels include gellan gum and its derivatives (eg., deacetylated gellan gum). Upon exposure to cations at physiological concentrations within the nasal cavity (notably Na^+, K^+, Ca^{2+}), glucuronic acid units in these polymers undergo cation chelation, facilitating double helix formation that subsequently crosslinks into three-dimensional gel networks. This process typically completes within seconds, demonstrating rapid responsiveness.[36,37]

Gellan gum concentration exhibits a positive correlation with gel strength. Studies demonstrate that a 0.2% gellan gum solution complexed with ceftriaxone (designated CFT-GG 0.2%) forms gels with optimal mucoadhesion and sustained-release properties upon contact with simulated nasal fluid.[38] Notably, divalent cations (Ca^{2+}) exhibit markedly superior gelation efficiency compared to monovalent sodium ions (Na^+), attributable to their enhanced crosslinking capacity.[36]

Ion-sensitive gels offer distinctive advantages for nasal delivery: 1) Physiological specificity: Gelation is highly contingent upon the nasal physiological environment, minimizing performance variability due to interindividual differences. 2) Enhanced retention: The resultant gels exhibit superior mucoadhesion, effectively resisting mucociliary clearance.[1] In a study of amoxicillin trihydrate mucoadhesive in situ nasal gel, formulations containing 0.3% w/v gellan gum demonstrated optimal mucosal retention properties, rendering them particularly indicated for localized treatment of sinus infections.[29]

pH-Sensitive Gels

pH-sensitive gels typically utilize polyelectrolyte materials such as carbopol or chitosan. These polymers contain abundant ionizable functional groups (eg., carboxyl, amino groups) that undergo pH-dependent ionization, governing macromolecular chain extension/coiling and hydration states.[39] Exemplified by Carbopol 934: At low pH (<4), Carboxyl groups remain predominantly protonated, maintaining coiled molecular conformations. At nasal physiological pH (5.5-–6.5), Carboxyl ionization generates negative charges, inducing chain extension through electrostatic repulsion. This facilitates water absorption and swelling, ultimately forming gels.[40]

The gelation kinetics of these systems are co-governed by environmental pH and ionic strength. For instance, a pH-sensitive nasal gel formulation containing ribavirin employs a composite matrix of 0.5% w/v gellan gum and 2% w/v poloxamer 124. This system forms sustained-release gel networks under nasal pH conditions, exhibiting drug release conforming to first-order kinetics.[41] Chitosan-based gels attract significant interest due to their bioadhesive properties and mucosal penetration enhancement. However, their application requires careful consideration of pH-dependent solubility constraints – achieving dissolution exclusively under acidic conditions.[6]

Enzyme/Biomolecule-Responsive Gels

Enzyme/biomolecule-responsive gels represent an innovative advancement in nasal drug delivery systems. These gels comprise biocompatible polymers whose crosslinked structures undergo selective "unlocking" upon recognition of enzymes (eg., matrix metalloproteinases) or biomolecules (eg., glutathione at pathological concentrations) uniquely present in nasal pathologies.[42] Under physiological conditions, the gel maintains structural integrity, securely encapsulating therapeutic agents-including peptides, proteins, nucleic acids, or small molecules.[43] Upon encountering target enzymatic or biomolecular signals, the network exhibits intelligent responses: either rapid dissolution or substantial swelling, enabling spatiotemporally precise and dosage-controlled drug release.[44]

This intelligent responsiveness confers significant advantages for nasal drug delivery:[42,43,45] 1) Targeted release: Drug liberation is exclusively triggered at pathological sites (eg., inflammatory or tumor microenvironments), minimizing off-target tissue irritation. 2) Extended residence: Mucoadhesive properties prolong nasal mucosal retention time, overcoming rapid clearance limitations inherent to conventional solutions. 3) Drug protection: The gel matrix provides a physical barrier that shields labile macromolecules (eg., insulin, vaccine antigens) from enzymatic degradation prior to release. 4) Enhanced delivery efficiency: Leveraging the nasal cavity's vascular density and first-pass metabolism avoidance, bioavailability is substantially increased-particularly advantageous for central nervous system (CNS) therapeutics (eg., Parkinson's disease medications). Integrating intelligence, high biocompatibility, and potent delivery capabilities, enzyme/biomolecule-responsive gels are emerging as pivotal platforms for nasal administration of innovative therapeutics-especially biologics and CNS drugs-thereby forging new pathways for precision medicine.

Comparative Performance of Different Stimuli-Responsive Systems

While all four types of NISG achieve sustained release, their performance characteristics differ in ways that guide material selection for specific applications. Thermosensitive systems (eg., poloxamers) offer well-defined transition temperatures and tunable gelation kinetics, but their gel strength and release profiles are sensitive to polymer concentration and may require co-formulation with other polymers to avoid irritation at high concentrations. Ion-sensitive systems (eg., gellan gum) provide rapid gelation (5–20 s) and strong mucoadhesion, making them particularly suitable for localized antibiotic delivery, although gel strength depends on local ionic strength which may vary across individuals. pH-sensitive systems (eg., carbomers, chitosan) offer high biocompatibility and can be designed to release drugs

specifically at inflamed nasal mucosa (pH 5.5–6.5), but their performance can be affected by interindividual pH variations. Enzyme-responsive systems represent the most targeted approach, releasing drugs only upon encountering pathological biomarkers, yet their clinical translation is currently limited by the need for consistent enzyme expression at the target site. From a drug delivery efficiency perspective, thermosensitive and ion-sensitive systems have been most extensively validated in preclinical models, while pH-sensitive and enzyme-responsive systems offer greater specificity but require further optimization for robust in vivo performance.

Drug Release Mechanisms and Delivery Efficiency Optimization

The material design strategies described above directly determine how drug is released from the gel network. Drug release from NISG constitutes a multifactor-regulated process involving interconnected mechanisms: gel matrix erosion, drug diffusion, and mucosal permeation. Comprehensive understanding of these mechanisms is paramount for optimizing delivery efficiency, particularly in sophisticated therapeutic applications such as CNS-targeted delivery. In NISG, release typically follows a diffusion-erosion synergistic mechanism, where the drug initially diffuses out through the gel network pores, followed by gradual transition to erosion-controlled release as the polymer matrix degrades. The following subsections detail these processes and their modulation.

Diffusion-Erosion Synergistic Release Mechanism

During the initial phase, drug liberation occurs predominantly through diffusion from gel network pores, exhibiting rapid release kinetics. Over time, matrix erosion progressively becomes the dominant mechanism, resulting in attenuated release rates.[36,46] Studies demonstrate that the in vitro release profile of mirtazapine-loaded thermosensitive nasal gel exhibits high concordance with its erosion curve, with both processes adhering to zero-order kinetics-indicating erosion-controlled drug release behavior.[28]

To further optimize these diffusion and erosion processes for precise delivery, release kinetics can be actively modulated through three primary integrated approaches:

Matrix modification: Incorporating mucoadhesive materials like Carbomer® 940 delays gel erosion.[47] Experimental data confirm that 0.17% w/v Carbomer 940 prolongs poloxamer gel erosion time by approximately 40%.[48]

Nano-complexation: Pre-encapsulating drugs within nanocarriers (eg., liposomes, nanoparticles) followed by dispersion in gel matrices enables dual-controlled release.[49] Such as the vinpocetine-loaded chitosan nanoparticle transfersomes-in-situ gel system achieved exceptional encapsulation efficiency (97.56 ± 1.23%) and drug loading capacity (61.04 ± 0.85%). In vivo pharmacokinetic studies demonstrated that nasal administration of this formulation, near-doubled maximum brain concentration (C_{max}) versus oral delivery ($p < 0.05$), significantly increased brain $AUC_{0\text{-}t}$ ($p < 0.05$), reduced systemic vinpocetine exposure by 63%, histopathological evaluation of nasal mucosa confirmed absence of irritation or toxicity, establishing formulation safety for nasal administration.[50]

Crosslinking density modulation: Regulating polymer concentration or incorporating crosslinking agents (eg., Ca^{2+}) enables precise control of gel network density, thereby governing drug diffusivity and release kinetics.[51]

Innovative Strategies for Brain-Targeted Delivery

To address the unique challenges of CNS delivery, researchers have developed innovative strategies optimizing drug transport efficiency via the nose-to-brain pathway:

Receptor-mediated transcytosis represents a cutting-edge approach. Surface functionalization of nanocarriers with targeting ligands (eg., peptides, proteins) significantly enhances drug accumulation in brain tissues.[1] A paradigm case is RVG29-modified rifampicin transfersomes: The RVG29 peptide specifically binds neuronal nicotinic acetylcholine receptors (nAChRs), facilitating axonal transport along the olfactory pathway for active targeting of dopaminergic neurons. This system achieves a brain targeting index 2.8-fold higher than non-targeted formulations.[52]

Nanocarrier-gel composite systems synergize dual advantages of nanotechnology and in situ gel platforms. Exemplified by the ceftriaxone-loaded albumin nanoparticle-gellan gum gel system, this integrated approach delivers multifaceted benefits: Enhanced transmucosal transport: Albumin nanoparticles facilitate drug permeation across nasal epithelium via gp60 receptor-mediated transcytosis. Optimized olfactory deposition: Gellan gum matrix provides

superior nasal retention, with 3D-printed nasal cast studies confirming >50% increased deposition in olfactory regions. Exceptional drug stability: Nanoparticle encapsulation efficiency of 98.86 ± 0.75% ensures structural integrity throughout sustained release. Collectively, this system ensures targeted CNS delivery while maintaining pharmaceutical stability during release.[38]

Rational utilization of permeation enhancers is pivotal for augmenting nasal mucosal drug permeation. Studies confirm that 3.0% w/v dimethyl-β-cyclodextrin (DM-β-CD) significantly enhances the transnasal permeation of carfentanil.[53] The primary mechanisms involve: reversible perturbation of epithelial tight junctions, increased apparent solubility of lipophilic drugs and reduced diffusion resistance across the mucus layer.[54]

Release Kinetics-Pharmacodynamic Correlations

Establishing in vitro-in vivo correlations is essential for formulation optimization. Studies reveal distinct therapeutic profiles aligned with release kinetics:

Rapid-release gels (T_{max}≈0.1 h): Rapid-release formulations are indicated for therapeutics requiring immediate onset (eg., antidepressants). In pharmacokinetic studies, the C_{max} in the brain following a single nasal administration of escitalopram oxalate-loaded chitosan nanoparticles in situ gel was 4.67 folds higher than the oral solution. The total $AUC_{0\text{-}12}$ in situ gel was 3.40 times higher than the intranasal drug solution and 13.31 times higher than an oral solution. The mean residence time for the brain's chitosan nanoparticles in situ gel was higher than intranasal drug and oral solutions.[55]

Sustained-release gels (release duration > 8 h): Suited for chronic therapies (eg., hormone replacement). The fluticasone-loaded zein nanoparticle-gel system achieves extended drug release exceeding 12 h.[56]

Pulsatile-release gels: Employing stimuli-responsive materials (eg., pH/temperature/ion-sensitive polymers) to enable triggered release under specific physiological conditions. Particularly applicable for circadian rhythm disorders requiring timed drug administration.[57,58]

Clinical Advancements and in vitro/in vivo Efficacy Validation in Drug Delivery

While foundational studies have detailed the material advantages and methodologies for preparing NISGs, recent research advancements decisively focus on their practical drug delivery applications. The correlations between release kinetics and therapeutic outcomes are increasingly borne out in targeted preclinical and clinical studies across multiple disease areas. Specifically, extensive in vitro and in vivo assays have validated that these formulations offer measurable improvements in drug release profiles, enhanced mucosal permeation, and elevated targeted bioavailability. Driven by these quantifiable delivery improvements, research is steadily transitioning from rigorous animal models to clinical trials, providing robust evidence for the technology's potential to optimize therapeutic efficacy, improve safety profiles, and increase patient compliance (Table 2).

Central Nervous System Disease Treatment

The nose-to-brain delivery advantages of NISGs are profoundly demonstrated in in vivo models of CNS disorders, where these systems successfully overcome the blood-brain barrier to significantly improve localized drug concentrations.

For depression management, an agomelatine-loaded Brij®-enriched liposomal in situ gel exhibited superior antidepressant efficacy in chronic restraint stress (CRS) rat models. In vivo behavioral assays demonstrated that treated rats achieved an 80.73% sucrose preference rate (significantly elevated from the baseline <60% in depressive models) and a reduced novel-suppressed feeding latency of 5.86 minutes compared to controls. Furthermore, biochemical assays revealed a substantial recovery of hippocampal neurotransmitters, including serotonin (44.92 ng/g), dopamine (50.42 ng/g), and brain-derived neurotrophic factor (BDNF, 50.92 pg/g).[62] Similarly, in vivo pharmacokinetic assays of an escitalopram oxalate-loaded chitosan nanoparticle in situ gel confirmed highly efficient nasal-brain transport. Following a single nasal administration, the maximum brain concentration C_{max} was 4.67-fold higher than that of an oral solution. Moreover, the total $AUC_{0\text{-}12}$ was 3.40-fold higher than a conventional intranasal solution and 13.31-fold higher than an oral solution, demonstrating a notably prolonged mean residence time in the brain.[55]

Groundbreaking drug delivery enhancements have also been achieved in Parkinson's Disease (PD) research, where sustained release is critical. A hydrogel platform engineered by compositing honokiol nanocrystals with a thermosensitive

Table 2 Nasal in situ Gel Formulations Under Investigation

Pharmaceutical Agent	Gel Type	Application Area	Research Phase	Primary Advantages	Key Research Findings
Ceftriaxone-albumin nanoparticle gel	Ion-sensitive (Gellan gum)	Bacterial meningitis	Preclinical (Large animal models)	Enhanced brain-targeted delivery	50% increase in olfactory region deposition; maintained antimicrobial activity; enhanced BBB permeability[38]
Amoxicillin trihydrate gel	Ion-sensitive (Gellan gum)	Acute bacterial sinusitis	Phase I/II clinical trial	Elevated local concentration, reduced systemic side effects	2.7-fold increase in mucosal retention; local effective duration >6 h[29]
Resveratrol nanosuspension gel	Ion-sensitive (Gellan gum)	Alzheimer's disease	Preclinical (Pharmacokinetics)	Direct nose-to-brain transport bypassing BBB	2.88-fold increase in brain bioavailability, drug targeting efficiency (458.2%), direct transport percentage (78.18%)[59]
Lorazepam gel	Ion-sensitive (Gellan gum/ Carbopol 934)	Antiepileptic therapy	Preclinical (Pharmacodynamics)	Rapid onset, reduced mucociliary clearance	Cumulative drug release: 97.32 ± 1.35% over 6 h[60]
Paroxetine gel	Ion-sensitive (Hydroxypropyl-β-cyclodextrin)	Depression	Preclinical (Pharmacokinetics)	Accelerated onset, elevated target site (brain) concentration	Drug content: 99.29%, cumulative release: 83.79%, Cmax: 870 ng/mL, Tmax: 0.5 h[61]
Agomelatine liposomal gel	Thermosensitive (Poloxamer/ hydroxypropyl methylcellulose, HPMC)	Depression	Phase I clinical trial	Improved bioavailability	30-50% increase in cerebral neurotransmitters, significant behavioral improvement[62,63]
Duloxetine gel	Thermosensitive (Pluronic F-127)	Depression	Preclinical (Pharmacodynamics)	Improved bioavailability	1.27-fold increase in drug permeation, 1.96-fold improvement in brain bioavailability[64,65]
Fluticasone propionate nanoparticle gel	Dual-responsive (Thermo-/Ion-sensitive)	Allergic rhinitis	Phase II clinicaltrial	Sustained anti-inflammatory action, tissue repair promotion	>70% nasal mucosal healing rate, 60% reduction in MMP9 expression[56]
Rasagiline mesylate gel	Thermosensitive (Poloxamer/ Carbopol 934/Chitosan)	Parkinson's disease	Preclinical (Pharmacokinetics)	Improved bioavailability	4 to 6-fold increase in bioavailability[66]
Galantamine-thiolated chitosan NP/poloxamer gel	Thermosensitive (Poloxamer/ Thiolated chitosan)	Alzheimer's disease	Preclinical (Pharmacodynamics)	Superior biocompatibility and brain targeting	Sustained release: 96%, encapsulation efficiency: 40%, high mucoadhesive strength, prolonged mucosal retention[67]
Ciprofloxacin gel	Thermosensitive (Poloxamer)	Local infections (eg., chronic sinusitis)	Preclinical (Pharmacokinetics)	Prevention of systemic and CNS adverse effects	Sustained drug release, prolonged nasal residence time[68]
Levofloxacin gel	Thermosensitive (Poloxamer)	Local infections (eg., chronic sinusitis)	Preclinical (Pharmacokinetics)	Prevention of systemic and CNS adverse effects	Higher pharmacokinetic exposure parameters ($C_{max/dose}$, $AUC_{0\text{-}inf/dose}$ or $AUC_{all/dose}$) compared to IV delivery[69]
Doxepin gel	Thermosensitive (Chitosan/β-Glycerophosphate)	Depression	Preclinical (Pharmacodynamics)	Improved bioavailability	Robust mucoadhesion; enhanced drug permeation, extended release profile, absence of local toxicity[70]
Metoprolol tartrate gel	pH-sensitive (Carbopol/ Hydroxypropyl methylcellulose, HPMC)	Cardiovascular disorders	Preclinical (Pharmacokinetics)	Improved bioavailability	Prolonged mucosal residence, improved permeation, avoidance of first-pass metabolism[71]
Donepezil hydrochloride gel	pH-sensitive (Chitosan)	Alzheimer's disease	Preclinical (Pharmacokinetics)	Improved bioavailability and brain targeting	46% and 39% increase in mean Cmax and AUC, 107% increase in mean brain drug content[33,72]
Escitalopram gel	pH-sensitive (Carbopol/ Hydroxypropyl methylcellulose, HPMC)	Depression	Preclinical (Pharmacokinetics)	Rapid onset, potent brain targeting	4.67-fold higher C_{max} vs. oral solution, 3.4-fold greater total AUC[55]
Asenapine maleate gel	pH-sensitive (β-Cyclodextrin /Poloxamer 407)	Schizophrenia	Preclinical (Pharmacokinetics)	Improved bioavailability	2.5-fold increase in bioavailability[73]
Paliperidone gel	pH-sensitive (Carbopol 934/ Hydroxypropyl methylcellulose, HPMC)	Schizophrenia	Preclinical (Pharmacodynamics)	Improved bioavailability	Controlled drug release, enhanced mucoadhesive properties[74]

matrix successfully normalized reactive oxygen species (ROS) and adenosine triphosphate levels within dopaminergic neuronal mitochondria. In vivo evaluations confirmed that this specific delivery system reversed mitochondrial dysfunction and improved behavioral motor skills in PD mice without inducing peripheral adverse effects.[75] Similarly, an RIN thermosensitive gel effectively repaired motor function impairment and mitigated oxidative stress and substantia nigra neuronal damage caused by PD.[76] Additionally, an ion-activated gellan gum in situ gel delivering chrysin demonstrated that prolonged mucosal retention effectively supports sustained free radical scavenging and the restoration of antioxidant enzyme activity, presenting a highly efficient delivery platform for neuroprotection.[77]

Significant formulation optimizations have also been validated for cognitive enhancement. A vinpocetine-loaded NISG achieved an approximately 20-fold enhancement in drug solubility and strengthened mucoadhesive properties. These delivery improvements directly resulted in prolonged nasal residence time, augmented drug distribution in brain tissue, and crucially, reduced systemic exposure. In vivo behavioral evaluations using the Morris water maze assay demonstrated a statistically significant improvement in spatial memory among treated rats, evidenced by a markedly shortened escape latency compared to model controls.[50,78]

Enhanced in vitro and in vivo Efficacy for Localized Infections

In the management of localized nasal infections, the inherent mucosal retention properties of in situ gels serve as a critical drug delivery mechanism that substantially enhances antibiotic bioavailability. Ex vivo and in vivo assays confirm that this targeted delivery approach achieves optimal therapeutic concentrations at infection sites while drastically minimizing systemic exposure.

A landmark advancement in brain-targeted delivery for bacterial meningitis has been validated through robust in vitro delivery models. A ceftriaxone-loaded albumin nanoparticle-gellan gum gel demonstrated significantly enhanced permeation flux in the in vitro BBB-PAMPA assay. Furthermore, drug deposition assays using 3D-bioprinted human nasal cavity models revealed a >50% higher deposition in the olfactory region (52.7 ± 3.8% vs. 34.2 ± 2.9% in controls). Crucially, in vitro microbiological assays confirmed that the formulation maintained uncompromised antimicrobial activity following this enhanced delivery process, showing potent minimum inhibitory concentrations against key pathogens: Streptococcus agalactiae (MIC 0.06 μg/mL), Haemophilus influenzae (MIC 0.12 μg/mL), and Neisseria meningitidis (MIC 0.03 μg/mL).[38]

Research on acute bacterial sinusitis treatment further confirms the quantifiable delivery advantages of in situ gels. Ex vivo mucosal permeation and retention assays of an amoxicillin trihydrate mucoadhesive in situ gel demonstrated predominant drug retention at mucosal surfaces with minimal systemic permeation. Key drug delivery improvements include a 2.7-fold higher mucosal retention versus conventional solutions and sustained local therapeutic concentrations exceeding 6 hours.[29] This extended release profile directly translates to significantly reduced adverse effects attributable to diminished systemic absorption.

Significant in vitro and in vivo delivery advancements have also emerged in the therapeutic management of fungal sinusitis. Drug release assays of a voriconazole-loaded clove oil transferosomal in situ nasal gel demonstrated sustained release kinetics, successfully liberating 82.5% of the voriconazole payload within 12 hours. This targeted delivery formulation achieved a 5.4-fold increase in drug permeability compared to controls. Concurrent in vitro assessment revealed a potent antifungal inhibition zone of 21.76 mm, while in vivo safety assays exhibited no discernible nephrotoxicity.[29] Furthermore, delivery assays evaluating an amphotericin B (AMB)-loaded nano-transferosome in situ gel achieved a high entrapment efficiency of 84.30%. In vitro evaluation against Aspergillus flavus yielded a 16.0 mm inhibition zone, while in vivo safety assays reported serum creatinine levels of 0.1197 mmol, indicating a drastically reduced renal impact. The gel's ability to facilitate the release of 79.25% of the encapsulated AMB and substantially enhance trans-nasal membrane permeability confirms its vital role in augmenting antifungal activity while mitigating drug-associated toxicity.[79]

Improved Drug Delivery and Efficacy in Inflammatory and Allergic Conditions

For localized inflammatory disorders such as allergic rhinitis, topical in situ gels overcome rapid clearance barriers, offering distinct drug delivery advantages. By maintaining prolonged localized anti-inflammatory effects, these targeted delivery platforms significantly reduce the propensity for systemic adverse effects.

Extensive in vivo therapeutic efficacy assays demonstrate how these formulations directly translate sustained drug release into measurable clinical improvements. An in vivo rat model assay evaluating a fluticasone propionate-loaded zein protein nanoparticle-in situ gelling system (FP-ZNPs-gel) demonstrated superior drug delivery outcomes compared to the conventional marketed product Flixonase®. This novel sustained-release formulation achieved an approximately 70% reduction in inflammatory cell infiltration within the nasal mucosa after 7 days of treatment, alongside a significant alleviation of mucosal edema. Furthermore, biochemical assays revealed an over 60% decrease in MMP9 levels—a key mediator intricately associated with tissue remodeling and inflammatory processes. In vivo histopathological evaluations confirmed that treatment with this specific delivery system largely restored the normal architecture of the nasal mucosa, an improvement directly attributed to optimized local drug retention.[56]

Similarly, in vivo immunological assays utilizing an allergen challenge model validated the delivery enhancements of a thermosensitive in situ gel loaded with mometasone furoate (formulated with Poloxamer 407 and Carbopol 974 P). This targeted delivery system significantly attenuated nasal symptoms and reduced ovalbumin-specific serum immunoglobulin E (IgE) levels. Furthermore, in vivo histological assessments confirmed that the sustained release of mometasone furoate markedly ameliorated manifestations of inflammation, successfully preventing vascular dilation, eosinophil infiltration, and the loss of epithelial cilia within the nasal mucosa.[18,80]

Crucial in vitro and ex vivo delivery assays have also driven advancements in anti-asthmatic interventions. A novel mucoadhesive in situ gel developed for the nasal delivery of salbutamol sulfate was evaluated through in vitro drug release assays, which recorded an exceptional 97.34% sustained drug release over an 11-hour period. This prolonged release profile significantly enhances therapeutic efficacy, while concurrent ex vivo permeation and histopathological assays detected no evidence of tissue damage, thereby confirming the safety and high translatability of this mucoadhesive drug delivery platform.[81]

In vitro and in vivo Safety Evaluation Framework

While the therapeutic efficacy of NISGs is well documented across multiple indications, establishing a rigorous safety profile through in vitro, ex vivo, and in vivo toxicity assays is equally critical for successful clinical translation. Local safety assessments primarily focus on ciliary toxicity and mucin interactions. Ciliary toxicity represents the most direct safety indicator, commonly evaluated using ex vivo toad palate and in vivo rat models.[82,83] In vivo safety assays demonstrate that appropriately designed in situ gels, such as ketamine formulations incorporating hydroxypropyl-β-cyclodextrin (HP-β-CD) as a permeation enhancer, induce only transient and reversible inhibition of ciliary motility without increasing overall toxicity. Conversely, formulations relying on alternative enhancers—specifically disodium edetate (EDTA), propylene glycol (PG), or Tween-80—may inflict irreversible ciliary damage.[84] Furthermore, in vitro mucin interaction analyses reveal that anionic polymers (eg., Carbomer) form strong electrostatic bonds with mucin, warranting strict vigilance regarding their potential impact on mucosal barrier function during long-term administration.[85,86]

Beyond localized mucosal effects, systemic toxicity assessments necessitate the careful evaluation of permeation enhancers and nanomaterials. For instance, cyclodextrin derivatives (eg., dimethyl-β-cyclodextrin, DM-β-CD) are generally proven safe at concentrations of ≤3% (w/v) in in vivo evaluations; however, excessive concentrations risk inducing cholesterol dissolution within the plasma membranes of mucosal epithelial cells.[53] Similarly, while nanocarriers such as albumin nanoparticles and liposomes typically exhibit highly favorable biocompatibility in in vitro assays, the degradation products from synthetic polymers like poly(lactic-co-glycolic acid) (PLGA) can elicit localized acidic microenvironments that may compromise mucosal integrity.[87]

Currently, comprehensive long-term safety data remain relatively limited, though initial in vivo repeat-dose toxicology studies are highly promising. Existing 6-month evaluations indicate that poloxamer-based gels (at concentrations <20% w/v) demonstrate no significant systemic toxicity,[88] and gellan gum-based gels (at concentrations <0.5% w/v) elicit no detectable mucosal pathological alterations.[81] Moving forward, the clinical translation of advanced NISGs will require more extensive in vivo genotoxicity and immunogenicity assays, particularly for novel targeted delivery systems featuring surface-modified peptides.

Technological Bottlenecks in Industrialization and Challenges in Translational Medicine

Beyond safety considerations, the industrialization of NISG presents its own set of challenges (Table 3). Addressing these bottlenecks necessitates multidisciplinary collaborative innovation spanning material science, pharmaceutics, engineering, and clinical medicine.

Challenges in Stability During Scale-Up Production

The transition from laboratory-scale trials to industrial-scale manufacturing presents primary technical challenges in batch-to-batch consistency and long-term stability:

Gelation temperature shift in thermosensitive gels constitutes a common challenge in large-scale manufacturing. Research has demonstrated that poloxamer solutions may undergo formation of micellar aggregates during storage, resulting in an elevation of gelation temperature (up to 2–3°C).[96] Proposed mitigation strategies include: Optimization of thermal processing protocols (eg., water bath treatment at 85°C ± 2°C); Incorporation of stabilizers (eg., 0.1% EDTA); Strict control of oxygen content during the filling process (<0.5 ppm) to prevent polymer degradation.[97,98]

Nanocomposite gels face significant challenges in physical stability. Liposomal/nanoparticulate systems embedded within gel matrices are susceptible to aggregation, fusion, or drug leakage due to interfacial interactions with the polymeric network.[99] Proposed enhancement strategies encompass: Application of lyoprotectants (eg., 5% trehalose to preserve nanostructure integrity during lyophilization); Optimization of nanocarrier surface charge (where |zeta potential| >30 mV enhances electrostatic stabilization); Implementation of in situ gelation technology utilizing dual-chamber syringe systems for mixing immediately prior to administration.[100,101]

Sterilization process compatibility represents a critical barrier to industrialization. Thermolabile polymers (eg., poloxamer, gellan gum) exhibit intolerance to thermal sterilization methods.[102] Conversely, radiation sterilization may induce polymer degradation, exemplified by carbomer backbone cleavage.[102] Advanced solutions include: Development of aseptic online mixing systems (Sterile-filtered polymer and drug solutions are combined immediately prior to filling); Implementation of subcooled liquid filling technology (Gels maintain liquid state at 2–8°C during filling, undergoing gelation upon temperature equilibration to ambient conditions).[103,104]

Table 3 Key Technical Bottlenecks and Resolution Strategies in the Laboratory-to-Industrialization Translation

Technical Bottlenecks	Primary Challenges	Innovative Solutions	Representative Advances
Scalability	Poor batch-to-batch consistency; Inadequate long-term stability	Continuous-flow manufacturing; Lyoprotectant optimization; Dual-chamber syringe systems	Microfluidic fabrication of nanocarrier-gel composites;[89] Trehalose/EDTA-stabilized Poloxamer systems[90]
Sterilization processes	Degradation of thermolabile materials; Polymer chain scission by irradiation	Aseptic inline mixing; Supercooled liquid filling technology; Non-thermal sterilization	Dual-needle prefilled syringes (drug/gel matrix separation)[91]
Stability assessment	Gelation temperature drift; Nanocarrier aggregation	Accelerated testing with mathematical modeling; Cryogenic transport systems	Predictive modeling of gelation temperature[92]
IVIVC (In vitro-in vivo correlation)	Significant inter-species variability; Distortion in conventional release assays	3D-bioprinted nasal models; Biphasic release media; γ-scintigraphy tracking	Human nasal cast predicting olfactory deposition[38,93]
Regulatory standards	Lack of evaluation methodologies; Ambiguous bioequivalence criteria	In vitro permeation-retention integrated assessment; Local drug concentration endpoints	Draft monograph for nasal preparations (European Pharmacopoeia)[94]
Cost control	High-cost functional materials; Complex processes increasing expenses	High-efficiency targeted peptide expression; Continuous-flow manufacturing; Natural phospholipid substitution	Significant cost reduction using soy lecithin for transfersomes[95]

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Challenges in Establishing in vitro-in vivo Correlation

The development of robust in vitro-in vivo correlation (IVIVC) constitutes a fundamental requirement for formulation optimization and bioequivalence assessment. However, the material-specific properties of NISG present unique challenges:

In vitro release methodologies fail to adequately simulate the complex nasal milieu. Conventional paddle/basket apparatuses yield distorted drug release profiles due to sample flotation artifacts. While flow-through cells better approximate in vivo conditions, standardized protocols remain underdeveloped.[105] Emerging protocols recommend biphasic release media (upper mucin-simulating layer; lower serous fluid-mimicking phase), demonstrating enhanced predictive capability for nasal absorption of lipophilic drugs.[106]

The limitations of animal models are becoming increasingly prominent. Significant anatomical disparities exist between the nasal cavity structures of rodents and humans (olfactory epithelium area ratio: ~50% in rats vs. ~10% in humans). Although large-animal models such as rabbits and sheep exhibit closer anatomical approximation to humans, their utilization is constrained by prohibitively high costs.[107,108] Emerging alternatives integrate 3D-bioprinted human nasal models with organ-on-a-chip technology.[109] As demonstrated by Pina et al, such platforms have successfully predicted nasal deposition patterns of diazepam nanogels.[110]

Current bioanalytical methodologies require further advancement. Conventional pharmacokinetic studies face challenges in differentiating locally retained drugs from systemically absorbed compounds. Innovative approaches encompass: γ-scintigraphy imaging (eg., 99mTc-DTPA-labeled formulations demonstrating significantly prolonged nasal residence time);[111] Microdialysis sampling for real-time monitoring of drug concentrations at local nasal sites and in cerebrospinal fluid;[112] Molecular imaging techniques (utilizing PET/CT to track radiolabeled nanocarriers[113]).

Multidimensional Challenges in Translational Medicine

Beyond technical bottlenecks, the clinical translation of NISG confronts multidimensional challenges spanning regulatory science, cost containment, and patient compliance:

Regulatory standard gaps constitute a primary barrier. Currently, no targeted quality standards exist for NISG formulations, specifically regarding: Gelation performance evaluation (eg., standardized assay for gelation time); Rheological characterization (acceptance criteria for viscoelastic moduli), and bioequivalence assessment for locally acting drugs.[9,114] Innovative regulatory science approaches encompass: Establishing integrated in vitro permeation-retention evaluation platforms;[115] Developing specialized bioequivalence guidelines for nasal formulations (eg., adopting local drug concentration as endpoint metric);[116] Constructing physiology-based pharmacokinetic (PBPK) models to predict pharmacodynamic outcomes across demographic groups.[117]

Cost-containment pressures stem from premium materials and complex manufacturing. Target peptide modifications (eg., RVG29) incur production costs 5-to-8-fold higher than conventional formulations.[118] Aseptic filling processes impose additional manufacturing expenditures. Cost-reduction strategies include: Developing high-efficiency expression systems (eg., Pseudomonas aeruginosa and Staphylococcus aureus platforms for bioactive molecule production);[119] Optimizing nanocarrier compositions (substituting synthetic phospholipids with soy lecithin);[120] Implementing continuous-flow manufacturing (microfluidic fabrication of nanocarrier-gel composite systems).[99]

Enhancing patient acceptance necessitates addressing both usability and sensory experience. Surveys indicate approximately 30% of patients express concerns about malodor or irritation during nasal administration.[121] Optimization strategies comprise: Incorporating palatability enhancers (eg., menthol for odor masking); Refining isotonicity regulators (substituting sodium chloride with trehalose to mitigate irritation);[122] Developing prefilled portable applicators (unit-dose sterile packaging); Engineering thermo-adaptive formulations (maintaining stability at 4–30°C to enhance accessibility in tropical regions).[123]

Future Perspectives: Application Scenarios in the Precision Medicine Era

Addressing the above translational bottlenecks will unlock the full potential of NISG. Looking ahead, driven by precision medicine and technological innovations, NISG are evolving from universal delivery systems toward personalized, smart-responsive, and multifunctional platforms.

Personalized Precision Delivery Systems

Individualized formulations tailored to genetic polymorphisms and disease subtypes represent a pivotal future direction, but their development must be grounded in validated biomarkers and clinical data. Studies demonstrate that CYP enzyme genetic polymorphisms significantly modulate metabolic rates of tricyclic antidepressants,[124] and pharmacogenomics-guided NISG with programmable release kinetics have been proposed to achieve rapid, sustained, or biphasic release patterns.[1] For Parkinson's disease subtypes (eg., tremor-dominant vs. postural instability/gait difficulty variants), personalized gels incorporating distinct drug cocktails (levodopa/dopamine agonists) have shown improved motor control in preclinical models.[125]

Biomarker-responsive intelligent systems represent a cutting-edge research frontier. In epilepsy management, thermosensitive gels engineered to release antiepileptic drugs upon local pH decrease (resulting from lactate accumulation during preictal phases) have been validated in animal seizure models.[126] Alternatively, zinc-chelating systems activated by elevated Zn^{2+} concentrations (characteristic of epileptic foci) enable on-demand therapy.[83] For Alzheimer's disease, β-amyloid-responsive hydrogels releasing antibody therapeutics upon detection of Aβ oligomers are under preclinical evaluation.[127]

These examples illustrate that personalized NISG are not generic concepts but are increasingly supported by experimental validation.

Revolutionizing Macromolecule Delivery

The rapid advancement of antibody and nucleic acid therapeutics has positioned NISG as high-efficiency delivery platforms capable of overcoming critical biological barriers:

Vaccine applications: The COVID-19 pandemic demonstrated the transformative potential of mRNA technology. NISG protect mRNA against nuclease degradation while enhancing mucosal immune responses.[128] Preclinical studies reveal that thermosensitive gel-embedded lipid nanoparticles (LNP) loaded with Spike protein mRNA elicit mucosal IgA levels >3-fold higher than intramuscular vaccines, conferring superior respiratory protection.[129]

Antibody brain delivery breakthrough: Systemic administration of Alzheimer's monoclonal antibodies (eg., aducanumab) exhibits critically low brain efficiency (<1% brain uptake).[130] FcRn receptor-targeted nanoparticle-in-gel systems significantly enhance nasal-to-brain antibody transport. Animal studies demonstrate 7.9-fold greater brain AUC versus intravenous administration with this platform.[105,131]

Gene editing tool delivery: Trans-nasal delivery of CRISPR-Cas9 systems faces substantial hurdles including large hydrodynamic diameter (>10 nm) and strong anionic surface charge.[132] Novel cationic liposome-in-gel platforms with charge-reversal functionality overcome these barriers: Exhibiting positive surface charge at nasal pH (ζ-potential~+15 mV) for enhanced muco-adhesion; Reverting to physiological negative charge (ζ-potential~-5 mV) post-brain entry to minimize cytotoxicity, thereby enabling efficient and safe cerebral gene editing (editing efficiency >40% in hippocampal neurons).[82,133] These platforms have moved beyond proof-of-concept and are now being optimized for clinical translation.

Integrated Intelligent Responsive Systems

Multifunctional integrated platforms represent the future evolution:

Microneedle-gel hybrid systems: Combining tissue penetration of microneedles with sustained-release capability of gels. Dissolvable microneedle arrays (containing drugs in needle tips) coupled with thermosensitive gel matrices demonstrate: Microneedles perforate mucosal barriers for immediate drug release upon dissolution; Gel reservoirs provide continuous pharmacological supplementation.[134,135] This dual-modality system achieves 50% reduction in initial T_{max} (vs conventional gels) with 2-fold extended therapeutic duration.[136]

Closed-loop feedback systems: Integrating biosensing modules with on-demand drug release units. Exemplified by a diabetic neuropathy management system that continuously monitors cerebrospinal fluid (CSF) glucose levels to modulate intelligent insulin release. Animal studies demonstrate 90% reduction in hypoglycemic events incidence with this platform.[137,138]

Neuromodulation synergistic systems: Thermosensitive gels incorporating photothermal transducers (eg., gold nanorods) enable localized hyperthermia under near-infrared (NIR) laser irradiation. This simultaneously induces gel phase transition

(LCST~40°C) and reversibly opens tight junctions (ZO-1 protein modulation), enhancing drug permeation across the blood-brain barrier (BBB).[139] In Parkinson's disease models, levodopa-gold nanorod composite gels with NIR actuation significantly elevate cerebral drug concentrations (3.8-fold vs passive diffusion).[140]

Conclusion

As an innovative drug delivery platform, NISG overcome critical limitations of conventional nasal formulations through their stimuli-responsive properties and precision delivery capabilities. This comprehensive review synthesizes advances in: Material design strategies governing gelation dynamics; Drug release mechanisms dictating pharmacokinetic profiles; Clinical translation progress validating therapeutic efficacy; and translational medicine challenges spanning regulatory and manufacturing domains. Our analysis elucidates the profound influence of gelation kinetics (eg., temperature-triggered viscosity transitions) on delivery efficiency, affirms evidence-based therapeutic advantages (enhanced bioavailability, reduced dosing frequency) and safety profiles (mucosal integrity preservation) from clinical studies, and dissects key technological bottlenecks (scale-up reproducibility, sterility assurance) impeding industrial translation.

In foundational research advances, relatively mature design principles have been established for four major categories of material systems: thermo-responsive, ion-responsive, pH-responsive, and enzyme/biomolecule-responsive types. Investigations into drug release mechanisms have evolved beyond simple dissolution control towards a deeper understanding of synergistic diffusion-erosion mechanisms. Nanocomposite systems and targeted modification strategies have significantly enhanced brain-targeted delivery efficiency. In clinical translation landscape, multiple in situ gel formulations targeting central nervous system disorders, infectious diseases, and allergic diseases have progressed to various research stages, demonstrating significant therapeutic benefits and promising safety profiles.

Despite these advancements, successful industrialization and clinical translation require overcoming critical hurdles in scalable manufacturing processes, long-term stability control, in vitro-in vivo correlation (IVIVC) evaluation, and the establishment of robust regulatory standards. Addressing these issues necessitates deep interdisciplinary convergence across materials science, nanotechnology, pharmaceutical engineering, and clinical medicine.

Looking forward, future research should prioritize three key developmental trajectories: (1) personalized precision delivery systems guided by pharmacogenomics and biomarker-responsive materials; (2) macromolecule delivery platforms to overcome mucosal barriers for nasal vaccines, targeted antibodies, and gene editing tools; and (3) integrated intelligent responsive systems, such as microneedle-gel hybrids and closed-loop feedback devices. Through synergistic innovation integrating the "material-process-evaluation" triad, NISG technology is poised to achieve a transformative leap from laboratory promise to clinical value, ultimately enhancing therapeutic efficacy and improving patient quality of life.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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