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Review

Thermosensitive *In Situ* Nasal Gel Incorporating Chitosan Nanoparticles of Zolmitriptan for Migraine Management: Formulation Strategies, Optimization, and Characterization—A Review

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Abstract:
Migraine is a prevalent neurovascular disorder characterized by recurrent attacks of moderate to severe headache, frequently associated with nausea, vomiting, photophobia, and phonophobia, leading to substantial impairment in quality of life and socioeconomic burden. Conventional oral therapy with Zolmitriptan, a selective serotonin 5-HT1B/1D receptor agonist, is clinically effective for acute migraine management but suffers from limitations including hepatic first-pass metabolism, delayed gastric emptying during migraine episodes, variable bioavailability, and reduced patient compliance in nausea-associated attacks. Intranasal delivery has emerged as a promising non-invasive strategy capable of providing rapid systemic absorption and direct nose-to-brain transport, thereby improving onset of action and therapeutic effectiveness. Recent advances in nanotechnology and intelligent polymeric delivery systems have significantly expanded the scope of nasal formulations for antimigraine therapy. Chitosan nanoparticles have attracted considerable attention because of their mucoadhesive properties, biocompatibility, permeation-enhancing ability, and capacity for controlled drug release. Furthermore, incorporation of nanoparticulate systems into thermosensitive *in situ* gels offers additional advantages, including prolonged nasal residence time, temperature-triggered gelation, enhanced mucosal contact, and sustained drug release. The synergistic integration of chitosan nanoparticles with thermoreversible gel systems represents a highly promising platform for targeted intranasal delivery of Zolmitriptan. This review critically discusses the pathophysiological basis of migraine therapy, pharmaceutical limitations of conventional Zolmitriptan formulations, scientific rationale for nasal drug delivery, formulation strategies involving chitosan nanoparticles, thermosensitive gel systems, optimization methodologies, characterization parameters, and recent progress in translational intranasal antimigraine drug delivery research. Special emphasis is placed on formulation design principles that may improve bioavailability, brain targeting efficiency, and patient therapeutic outcomes.

Keywords: Migraine; Zolmitriptan; Intranasal delivery; Chitosan nanoparticles; Thermosensitive *in situ* gel; Nose-to-brain transport; Mucoadhesion

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1. Introduction

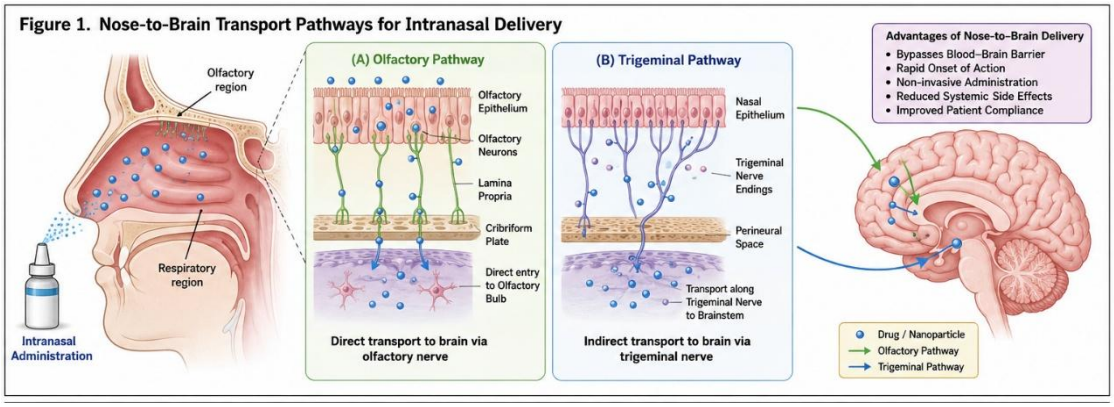
Migraine is among the most common disabling neurological disorders worldwide and represents a substantial public health burden because of its high prevalence, chronic recurrence, and marked impact on daily functioning **[1]**. Epidemiological evidence indicates that migraine affects nearly 15% of the global population, with higher prevalence among women than men, largely due to hormonal, genetic, and neurovascular factors **[2]**. Clinically, migraine is characterized by recurrent unilateral pulsating headache episodes lasting from 4 to 72 hours and frequently accompanied by nausea, vomiting, photophobia, phonophobia, and sensory hypersensitivity. In some patients, transient neurological disturbances known as aura precede headache onset **[2,3]**.

The pathophysiology of migraine is complex and multifactorial, involving activation of the trigeminovascular system, neurogenic inflammation, abnormal cortical excitability, and dysregulation of serotonergic neurotransmission pathways **[3]**. Release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), substance P, and neurokinin A contributes to meningeal vasodilation, plasma protein extravasation, and sensitization of nociceptive pathways, ultimately producing migraine pain **[4]**. Because serotonin receptors play a crucial regulatory role in cerebral vascular tone and pain signaling, serotonin receptor agonists (triptans) remain the cornerstone of acute migraine pharmacotherapy **[4,5]**.

Among triptan-class drugs, Zolmitriptan has emerged as an important second-generation antimigraine agent because of its high affinity for 5-HT1B/1D receptors, favorable lipophilicity, rapid onset of pharmacological action, and active metabolite formation **[5]**. However, oral delivery of Zolmitriptan is often associated with limitations such as delayed gastrointestinal absorption, reduced absorption during migraine-induced gastric stasis, hepatic first-pass metabolism, and variable systemic bioavailability, all of which can delay therapeutic response during acute migraine attacks **[5,6]**.

To overcome these limitations, intranasal delivery has gained substantial pharmaceutical interest because of its rapid absorption, avoidance of first-pass metabolism, non-invasive administration, and direct access to the central nervous system through olfactory and trigeminal neuronal pathways **[6,7]**. However, efficient nasal delivery requires overcoming physiological barriers such as mucociliary clearance, limited residence time, and enzymatic degradation. These challenges have stimulated the development of advanced nasal drug delivery systems including nanoparticle carriers, mucoadhesive polymers, and thermosensitive gel platforms **[7,8]**.

Chitosan nanoparticles are particularly promising due to their positive surface charge, biocompatibility, biodegradability, intrinsic mucoadhesiveness, and ability to transiently open epithelial tight junctions, thereby enhancing nasal permeation and drug absorption **[8,9]**. Additionally, thermosensitive *in situ* gels composed primarily of poloxamers remain liquid during administration but transform into gel at physiological nasal temperature, increasing retention time and reducing drug drainage from the nasal cavity **[9,10]**. The combination of nanoparticulate delivery with thermoreversible gel systems offers a dual-functional platform for enhanced intranasal therapy. Accordingly, this review focuses on the formulation strategies, optimization techniques, physicochemical characterization, and therapeutic prospects of thermosensitive *in situ* nasal gels incorporating chitosan nanoparticles of Zolmitriptan for migraine management.



2. Chitosan Nanoparticles as Advanced Intranasal Drug Carriers

Nanotechnology-based drug delivery systems have emerged as highly promising approaches for improving the therapeutic performance of central nervous system-active drugs delivered through the nasal route **[11,12]**. Among various polymeric carriers investigated, chitosan nanoparticles have attracted particular scientific attention because of their excellent biocompatibility, biodegradability, low immunogenicity, and intrinsic mucoadhesive properties, making them highly suitable for nasal administration **[13]**. Chitosan is a naturally occurring linear cationic polysaccharide obtained by deacetylation of chitin, primarily composed of β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units. The presence of protonated amino groups imparts positive surface charge to chitosan under acidic conditions, allowing electrostatic interaction with negatively charged mucosal surfaces **[13,14]**.

One of the most important pharmaceutical advantages of chitosan nanoparticles is their ability to prolong nasal residence time through strong mucoadhesion. Electrostatic interaction between positively charged chitosan and negatively charged sialic acid residues of nasal mucin enhances formulation retention at the site of administration, thereby increasing contact time for absorption **[14]**. Additionally, chitosan transiently opens tight junction proteins between epithelial cells, resulting in increased paracellular transport of hydrophilic and moderately lipophilic drugs across the nasal membrane **[15]**. This permeation-enhancing effect is particularly valuable for antimigraine drugs intended for rapid systemic absorption or direct brain targeting.

For Zolmitriptan delivery, chitosan nanoparticles provide multiple formulation advantages including drug encapsulation, protection against enzymatic degradation, controlled release behavior, enhanced permeability, and improved pharmacokinetic stability **[16]**. Nanometric particle size (typically 100–300 nm) offers high surface area, efficient mucosal interaction, and improved penetration through biological barriers. Furthermore, surface modification of chitosan nanoparticles with ligands or hydrophilic stabilizers can further enhance targeting efficiency and colloidal stability **[17]**.

The most widely employed preparation method for chitosan nanoparticles is ionic gelation, in which positively charged amino groups of chitosan interact with multivalent anions such as sodium tripolyphosphate (TPP), resulting in spontaneous nanoparticle formation under mild aqueous conditions without harsh organic solvents **[18]**. Ionic gelation offers several formulation benefits including simplicity, scalability, high encapsulation efficiency, and preservation of drug stability, making it highly suitable for sensitive intranasal formulations.

Recent studies have demonstrated that chitosan-based nanosystems significantly improve nasal absorption of CNS-active molecules and enhance brain targeting efficiency via olfactory and trigeminal transport pathways **[19]**. Therefore, incorporation of Zolmitriptan into chitosan nanoparticles represents a rational pharmaceutical strategy for rapid migraine relief with improved bioavailability and enhanced therapeutic response.

3. Thermosensitive *In Situ* Nasal Gel Systems

Thermosensitive *in situ* gel technology represents an advanced smart drug delivery platform designed to overcome rapid nasal clearance and short mucosal residence time associated with conventional liquid nasal formulations **[20]**. These systems remain in low-viscosity liquid form during administration, enabling easy instillation into the nasal cavity, but rapidly undergo sol-to-gel transformation upon exposure to physiological nasal temperature (~32–35°C), forming a semi-solid gel depot at the administration site **[21]**. This transition significantly prolongs mucosal contact time, minimizes formulation drainage, and supports sustained drug release.

Among thermogelling polymers, poloxamers are the most extensively investigated pharmaceutical excipients because of their excellent safety profile, non-irritancy, and reversible temperature-dependent micellization behavior **[21,22]**. Poloxamer 407, a triblock copolymer consisting of polyethylene oxide–polypropylene oxide–polyethylene oxide segments, exhibits thermoreversible gelation due to dehydration and aggregation of hydrophobic polypropylene oxide chains at elevated temperature, ultimately leading to three-dimensional gel network formation **[22]**. Poloxamer 188 is commonly incorporated as a gelation modifier to optimize gelation temperature, viscosity, and spreadability.

For intranasal delivery, ideal thermosensitive gel systems should possess gelation temperature close

to nasal physiological temperature, rapid gelation kinetics, suitable rheological behavior, good spreadability, non-irritancy, and prolonged retention capability **[23]**. However, poloxamer-only systems often suffer from weak mucoadhesion and relatively fast erosion. To address this limitation, incorporation of mucoadhesive polymers such as chitosan, carbopol, hydroxypropyl methylcellulose, or sodium alginate is frequently employed **[24]**.

The combination of chitosan nanoparticles with thermosensitive *in situ* gel offers synergistic pharmaceutical advantages. Chitosan nanoparticles enhance permeation and provide controlled drug release, while thermogelling matrices improve nasal retention and reduce clearance. This dual-functional approach may significantly improve intranasal delivery efficiency of Zolmitriptan, offering rapid onset alongside sustained therapeutic action **[24,25]**.

Table 1. Reported Intranasal Nanoparticulate / Gel-Based Antimigraine Delivery Systems

Drug	Delivery System	Polymer / Carrier	Major Outcome	Reference
Zolmitriptan	Mucoadhesive nasal insert	Chitosan–Chondroitin sulfate	Improved nasal residence and controlled release	**[26]**
Zolmitriptan	Nanoparticles	Chitosan	Enhanced permeation and bioavailability	**[27]**
medication	Thermosensitive nasal gel	Poloxamer + Chitosan	Rapid gelation and sustained release	**[28]**
medication	Nanoemulsion nasal gel	Mucoadhesive polymeric matrix	Increased brain targeting	**[29]**
medication	Polymeric nanoparticles	PLGA / Chitosan	Improved CNS delivery efficiency	**[30]**

4. Optimization Strategies for Thermosensitive Chitosan Nanoparticle Nasal Gels

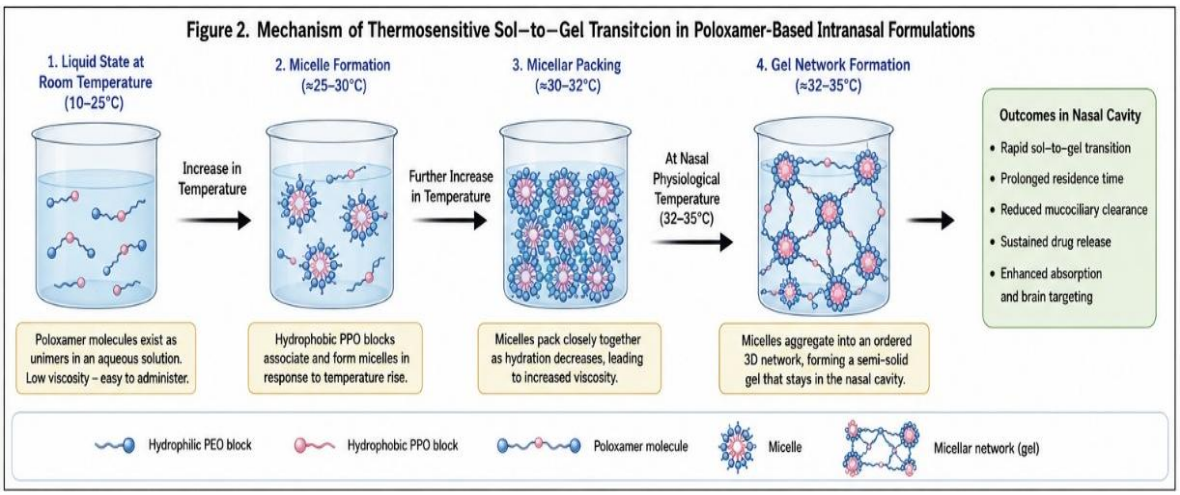
The successful development of thermosensitive *in situ* nasal gel systems incorporating chitosan nanoparticles depends strongly on systematic optimization of formulation variables that influence physicochemical stability, gelation behavior, mucoadhesion, drug release, and permeation performance **[31,32]**. Conventional one-factor-at-a-time experimentation is often inadequate because pharmaceutical formulations involve multiple interacting variables. Consequently, modern formulation development increasingly relies on **Design of Experiments (DoE)** and **Quality by Design (QbD)** approaches for robust optimization and scientific understanding of critical formulation parameters **[33]**.

In chitosan nanoparticle formulations, critical material attributes include polymer concentration, molecular weight of chitosan, degree of deacetylation, pH of preparation medium, chitosan-to-crosslinker ratio, and concentration of sodium tripolyphosphate (TPP) **[34]**. These variables directly influence particle size, zeta potential, encapsulation efficiency, colloidal stability, and drug release kinetics. For example, increasing chitosan concentration generally increases viscosity and entrapment efficiency, but excessive polymer concentration may produce larger particles due to aggregation **[35]**. Similarly, optimization of TPP concentration is essential because inadequate crosslinking leads to unstable nanoparticles, while excessive crosslinking may produce rigid particles with reduced drug diffusion.

For thermosensitive gel systems, polymer concentration is the primary determinant of gelation temperature and rheological behavior. Poloxamer 407 concentration controls micellar aggregation and gel formation temperature, whereas poloxamer 188 acts as a gelation modifier that improves formulation flexibility and adjusts viscosity **[36]**. Incorporation of mucoadhesive excipients such as chitosan, carbopol, or hydroxypropyl methylcellulose can further influence gel strength, residence time, and drug diffusion characteristics **[37]**. Therefore, optimization requires balancing injectability at room temperature with rapid gelation at nasal physiological temperature.

Factorial designs, Box–Behnken design, central composite design, and response surface methodology are widely used statistical tools for optimizing these complex formulations **[33,38]**. These approaches enable simultaneous evaluation of independent variables and their interactions on responses such as particle size, polydispersity index, zeta potential, entrapment efficiency, gelation temperature, viscosity, mucoadhesive strength, and cumulative drug release. Such statistical modeling

improves reproducibility, reduces experimental burden, and supports scale-up feasibility.



5. Characterization Parameters of Nanoparticle-Loaded Thermosensitive Nasal Gels

Comprehensive characterization is essential to establish formulation quality, performance, and translational suitability for intranasal delivery **[39]**. For chitosan nanoparticles, **particle size** and **polydispersity index (PDI)** are primary indicators of colloidal quality. Particle size below approximately 200–300 nm is generally desirable for improved mucosal interaction and enhanced penetration across biological barriers **[40]**. Low PDI values (<0.3) indicate narrow size distribution and better formulation homogeneity.

Zeta potential is another critical parameter reflecting nanoparticle surface charge and colloidal stability. Positively charged chitosan nanoparticles usually exhibit zeta potential values above +20 mV, which support electrostatic interaction with negatively charged mucin and improve mucoadhesion **[41]**. **Entrapment efficiency** determines the percentage of drug successfully incorporated within nanoparticles and influences release behavior, dose efficiency, and therapeutic performance.

Morphological characterization using **scanning electron microscopy (SEM)** and **transmission electron microscopy (TEM)** provides information on particle shape, aggregation state, and surface texture **[42]**. Spherical smooth particles with minimal aggregation are generally preferred for consistent pharmaceutical performance. Compatibility studies using **Fourier transform infrared spectroscopy (FTIR)**, **differential scanning calorimetry (DSC)**, and **X-ray diffraction (XRD)** help identify polymer–drug interactions and assess changes in crystallinity after encapsulation **[43]**.

For thermosensitive gels, **gelation temperature** is among the most important performance indicators. Ideal intranasal formulations should undergo phase transition near nasal physiological temperature (approximately 32–35°C), ensuring ease of administration and rapid gel formation after dosing **[44]**. **Viscosity and rheological studies** determine injectability, spreadability, and gel consistency. Pseudoplastic or shear-thinning behavior is particularly desirable because it enables easy administration while maintaining high viscosity after gelation **[45]**.

Mucoadhesive strength is critical for prolonging nasal retention and reducing mucociliary clearance. Enhanced mucoadhesion improves drug residence time and absorption efficiency **[46]**. Additionally, ***in vitro* release studies**, ***ex vivo* permeation studies**, and **nasal ciliotoxicity assessments** are essential to evaluate sustained release behavior, permeation enhancement, and mucosal safety of the developed system **[47]**.

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Table 2. Key Optimization Variables and Characterization Parameters for Chitosan Nanoparticle-Based Thermosensitive Nasal Gels

Category	Parameter	Pharmaceutical Significance	Preferred Range / Outcome
Nanoparticle Optimization	Particle size	Permeation and mucosal interaction	100–250 nm
	Polydispersity Index	Uniformity of particle distribution	<0.30
	Zeta potential	Stability and mucoadhesion	> +20 mV
	Entrapment efficiency	Drug loading capacity	>70%
Polymer Variables	Chitosan concentration	Mucoadhesion / permeability	Optimized statistically
	TPP concentration	Crosslinking density	Balanced for stability
Gel Optimization	Gelation temperature	Phase transition in nasal cavity	32–35°C
	Gel strength	Retention and spreadability	Moderate–high
	Viscosity	Administration + retention	Shear-thinning profile
Biological Performance	Mucoadhesion	Prolonged retention	High
	Permeation efficiency	Rapid absorption / brain targeting	Enhanced
Safety	Ciliotoxicity	Nasal mucosal compatibility	Non-irritant

6. Future Perspectives

The development of thermosensitive *in situ* nasal gels incorporating chitosan nanoparticles of Zolmitriptan represents a promising advancement in targeted migraine therapy; however, several opportunities remain for further scientific refinement and translational advancement **[48,49]**. Current formulation strategies primarily focus on improving nasal retention, permeation, and sustained drug release, but future investigations are expected to emphasize **precision brain targeting**,

stimuli-responsive delivery, and **patient-centric nasal dosage platforms**.

One important direction involves **surface engineering of chitosan nanoparticles** with targeting ligands, peptides, or receptor-specific moieties capable of enhancing selective uptake through olfactory neurons and trigeminal pathways **[50]**. Functionalized nanocarriers may significantly improve direct brain delivery efficiency while reducing systemic exposure and peripheral adverse effects. Similarly, incorporation of stealth polymers or hybrid polymer–lipid nanostructures may improve colloidal stability, mucus penetration, and controlled intracellular trafficking.

Emerging pharmaceutical technologies such as **Quality by Design (QbD)-guided formulation development**, **artificial intelligence-assisted optimization**, and **computational pharmacokinetic modeling** are expected to improve formulation predictability and accelerate translation from laboratory-scale development to industrial manufacturing **[51]**. Machine learning-based predictive models may help establish optimal relationships between polymer concentration, nanoparticle properties, rheology, release kinetics, and in vivo performance with reduced experimental burden.

Another promising area is the development of **multifunctional thermoresponsive biomaterials** that combine temperature sensitivity with pH responsiveness, enzyme-triggered release, or redox-sensitive drug liberation, thereby enabling highly controlled and disease-responsive intranasal therapy **[52]**. Such intelligent systems may provide rapid onset during acute migraine attacks while maintaining prolonged therapeutic coverage.

From a translational perspective, future work should increasingly focus on **in vivo pharmacokinetic studies**, **brain biodistribution imaging**, **long-term nasal safety assessment**, **mucosal tolerability**, and **clinical performance evaluation** in migraine patients **[53]**. Regulatory acceptance of intranasal nanoparticle formulations will depend strongly on reproducible manufacturing, scalability, sterilization compatibility, excipient safety, and clear demonstration of clinical superiority over conventional dosage forms.

Overall, the convergence of nanotechnology, smart polymer science, and intranasal brain-targeting strategies is expected to create next-generation antimigraine therapies with improved therapeutic efficiency, faster onset, lower dose burden, and superior patient adherence.

7. Conclusion

Migraine remains a highly prevalent and disabling neurological disorder requiring rapid and effective therapeutic intervention. Although conventional oral administration of Zolmitriptan remains clinically useful, limitations such as hepatic first-pass metabolism, delayed gastrointestinal absorption, variable bioavailability, and poor patient compliance during severe attacks highlight the need for improved delivery strategies **[3,5]**. Intranasal drug delivery offers an attractive alternative because of its rapid absorption, non-invasive administration, bypass of hepatic metabolism, and potential for direct nose-to-brain transport **[6,47]**.

This review highlights that **chitosan nanoparticles** represent highly effective carriers for intranasal delivery because of their mucoadhesive behavior, permeation-enhancing ability, biodegradability, and capacity for controlled drug release **[13,14]**. Furthermore, incorporation of these nanoparticles into **thermosensitive *in situ* gel systems** offers synergistic advantages by increasing nasal residence time, improving formulation retention, and enabling sustained therapeutic release at the site of administration **[23,44]**.

Optimization strategies using modern pharmaceutical design tools such as DoE and QbD have significantly improved formulation reproducibility and scientific understanding of critical quality attributes, while advanced characterization techniques provide essential insight into colloidal stability, rheological performance, mucoadhesion, and permeation behavior **[31,33]**. Collectively, published evidence suggests that thermosensitive *in situ* nasal gels containing chitosan nanoparticles of Zolmitriptan offer substantial promise as next-generation targeted antimigraine delivery systems.

Future translational studies involving preclinical pharmacokinetics, brain distribution analysis, long-term mucosal safety evaluation, and clinical validation will be essential to establish the therapeutic and commercial viability of these advanced pharmaceutical systems.

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Conflict of Interest

The authors declare no conflict of interest.

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