

pH-Triggered in-Situ Nasal Gel Systems for Migraine Therapy: A Review

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Abstract

Intranasal drug delivery has gained considerable attention as a non-invasive route for delivering drugs to both systemic circulation and the central nervous system, particularly for the treatment of migraine. Traditional nasal formulations – such as sprays and drops – often show poor therapeutic performance due to rapid mucociliary clearance and limited retention within the nasal cavity. To overcome these challenges, in-situ gel systems have been designed, which transform from a liquid to a gel state under physiological conditions, thereby improving residence time and drug absorption. pH-responsive in-situ nasal gels are especially advantageous as they undergo gelation at the physiological pH of the nasal cavity, resulting in enhanced mucoadhesion and prolonged drug release. The present review provides a critical overview of recent developments (2020–2025) in pH-triggered nasal gel systems with particular relevance to migraine therapy. Special attention is given to herbal therapeutic agents, such as ginger extract and peppermint oil, which possess notable anti-inflammatory and analgesic activities. In addition, the capability of these systems to facilitate direct nose-to-brain drug transport via olfactory and trigeminal pathways is discussed, emphasizing their significance in improving brain targeting efficiency. Although these systems show promising potential, certain limitations – such as formulation stability, variability in herbal components, and lack of extensive clinical validation – still exist. Therefore, further research is required to fully establish their clinical applicability. Overall, pH-responsive in-situ nasal gels containing herbal actives offer a promising approach for effective migraine management. This review uniquely emphasizes the integration of herbal therapeutics, such as ginger extract and peppermint oil with pH-triggered nasal gel systems, an area that remains relatively underexplored in current pharmaceutical research.

Keywords: Intranasal drug delivery, pH-responsive in-situ gel, nose-to-brain delivery, migraine therapy, ginger extract, peppermint oil, mucoadhesive polymers

INTRODUCTION

Intranasal drug delivery has emerged as a promising alternative route for both systemic and central

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nervous system (CNS) drug administration, particularly in the management of neurological disorders such as migraine [1]. This route offers several advantages, including rapid drug absorption, non-invasive administration, avoidance of hepatic first-pass metabolism, and improved patient compliance. The nasal cavity possesses a highly vascularized mucosal surface along with a relatively large surface area, which facilitates efficient drug permeation into systemic circulation [2]. However, the clinical effectiveness of conventional nasal formulations remains limited due to rapid mucociliary clearance, enzymatic degradation, and short residence time within the

nasal cavity, ultimately reducing therapeutic efficacy [3]. One of the most significant advantages of the intranasal route is its ability to enable direct drug transport to the brain through the olfactory and trigeminal nerve pathways. This unique nose-to-brain delivery mechanism allows drugs to bypass the blood–brain barrier, thereby enhancing therapeutic effectiveness in the treatment of CNS disorders [4].

Despite these advantages, conventional nasal dosage forms – such as drops, sprays, and solutions – are associated with poor retention and inconsistent drug absorption, necessitating the development of advanced drug delivery systems [5]. In this context, in-situ gel systems have gained considerable attention as an effective strategy for enhancing intranasal drug delivery [6]. These systems are administered as low-viscosity liquids and undergo a transformation into a gel upon exposure to physiological conditions such as pH, temperature, or ionic strength [7]. The resulting gel increases the residence time of the formulation within the nasal cavity, thereby improving drug absorption and prolonging therapeutic action [8].

Among various in-situ gel systems, pH-responsive formulations are particularly advantageous due to their compatibility with the nasal environment [9]. These systems remain in a sol state at acidic pH and undergo gelation when exposed to the physiological pH of the nasal cavity (approximately 5.5–6.5). The ionization of pH-sensitive polymers leads to the formation of a three-dimensional gel network, which enhances mucoadhesion and provides sustained drug release [10].

Furthermore, recent research has explored the incorporation of herbal therapeutic agents, such as ginger extract and peppermint oil, into nasal gel systems. These natural compounds exhibit significant anti-inflammatory, analgesic, and neuroprotective properties, making them promising candidates for migraine management. However, their integration into pH-responsive in-situ nasal gel systems remains relatively underexplored, highlighting the need for further investigation [11].

Therefore, the present review provides a comprehensive and critical evaluation of pH-triggered in-situ nasal gel systems for migraine therapy. It focuses on formulation strategies, mechanisms of gelation, and key evaluation parameters, along with recent advancements in the field. Particular emphasis is placed on the integration of herbal therapeutic agents, such as ginger extract and peppermint oil, for enhanced therapeutic efficacy. Furthermore, this review highlights existing research gaps, challenges, and future perspectives to facilitate the development of more effective and clinically translatable nasal drug delivery systems [12].

ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The anatomical and physiological characteristics of the nasal cavity play a crucial role in determining the efficiency of drug absorption and its potential for direct delivery to the brain [13]. The nasal route is particularly advantageous for rapid drug action due to its rich vascularization, large surface area, and unique connection to the central nervous system. These features make it a suitable pathway for both local and systemic drug delivery, especially in the treatment of neurological disorders [14].

Structure of Nasal Cavity

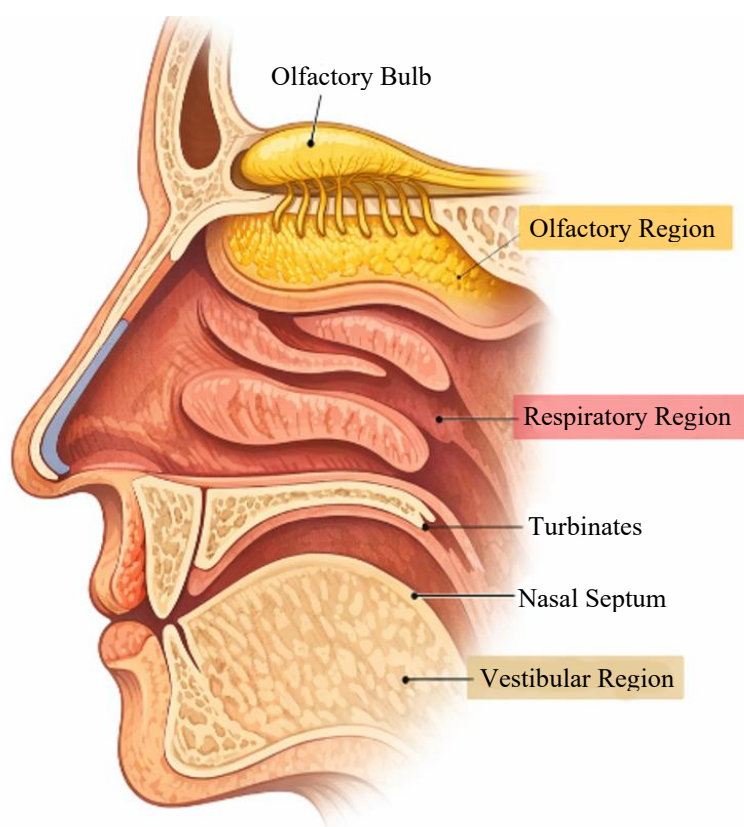
The nasal cavity is divided into two symmetrical halves by the nasal septum and extends posteriorly into the nasopharynx. It is lined with a mucosal membrane composed of pseudostratified ciliated columnar epithelium along with mucus-secreting goblet cells [15]. The mucus layer acts as a protective barrier by trapping dust particles and microorganisms, while the coordinated beating of cilia facilitates the clearance of mucus toward the nasopharynx. Although this mucociliary clearance mechanism plays a vital protective role, it also limits drug residence time within the nasal cavity, thereby reducing drug absorption and therapeutic effectiveness [16].

Functional Regions of the Nasal Cavity

The nasal cavity is divided into three distinct functional regions:

- **Vestibular Region:** The vestibular region is the anterior portion of the nasal cavity and is lined with stratified squamous epithelium along with nasal hairs (vibrissae). Its primary function is filtration of inhaled particles, and it contributes minimally to drug absorption [17].
- **Respiratory Region:** The respiratory region is the largest and most important area for drug absorption. It is highly vascularized and lined with ciliated columnar epithelium. The presence of nasal turbinates increases the surface area, enhancing drug–mucosa interaction and facilitating efficient absorption into systemic circulation [18].
- **Olfactory Region:** The olfactory region is in the upper part of the nasal cavity and is responsible for the sense of smell [19]. Importantly, it provides a direct pathway for drug transport to the brain via olfactory neurons. This region plays a critical role in nose-to-brain drug delivery and is particularly relevant for targeting central nervous system disorders [20].

The anatomy of the nasal cavity and major drug absorption regions are illustrated in Figure 1.



Anatomy of Nasal Cavity Showing Regions Involved in Drug Absorption

Figure 1. Anatomy of the nasal cavity showing drug absorption regions [21].

Mechanisms of Drug Absorption

Drug absorption across the nasal mucosa occurs through multiple pathways depending on the physicochemical properties of the drug:

- **Transcellular Pathway:** Lipophilic drugs diffuse through epithelial cell membranes [22].
- **Paracellular Pathway:** Small hydrophilic molecules pass through intercellular junctions [23].
- **Carrier-Mediated Transport:** Specific transport proteins facilitate drug uptake [24].
- **Endocytic Transport:** Macromolecules and nanoparticles are internalized via vesicular mechanisms [25].

The extent of absorption is influenced by factors such as molecular size, lipophilicity, solubility, and formulation characteristics. The various mechanisms of drug absorption across the nasal mucosa are illustrated in Figure 2.

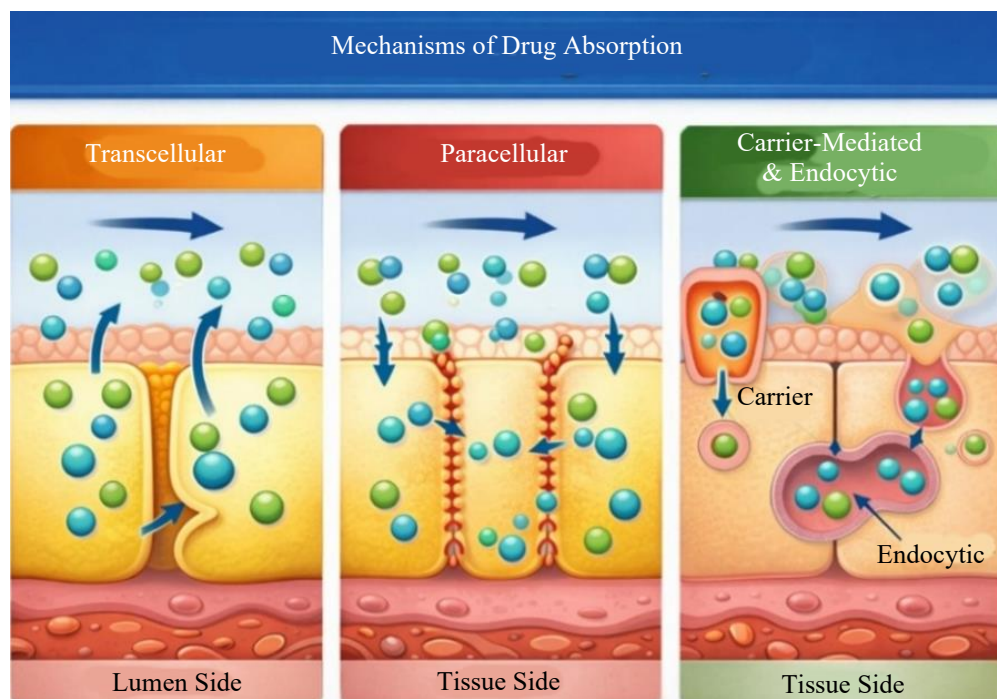


Figure 2. Mechanisms of drug absorption [26].

Nose-to-Brain Drug Transport

Intranasal administration enables direct drug delivery to the brain through two main pathways:

- *Olfactory Pathway*: Drugs are transported from the olfactory epithelium to the olfactory bulb and other brain regions [27].
- *Trigeminal Pathway*: Drugs reach the brainstem and deeper CNS structures via trigeminal nerve branches [28].

These pathways allow drugs to bypass the blood–brain barrier, resulting in rapid onset of action and improved therapeutic efficacy in neurological disorders such as migraine. The various pathways involved in nose-to-brain drug transport are illustrated in Figure 3.

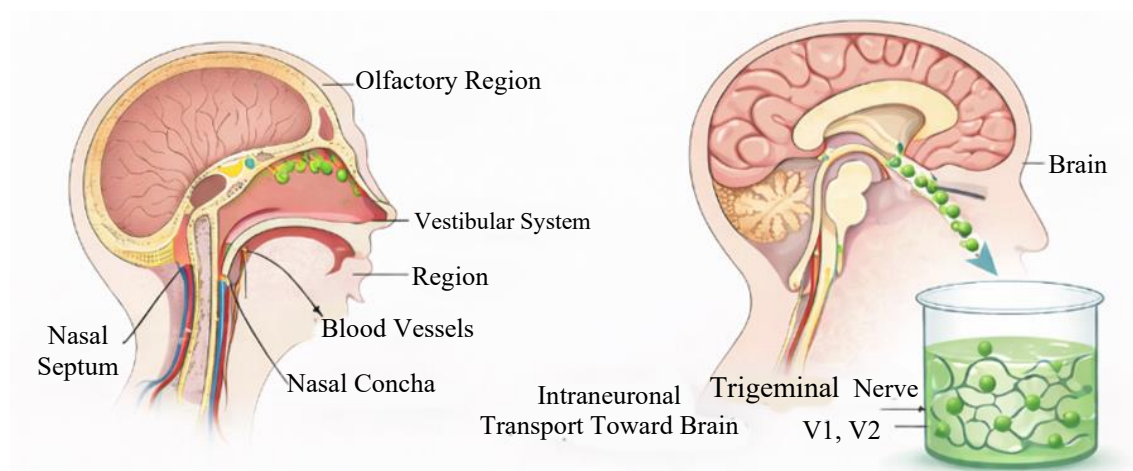


Figure 3. Nose-to-brain drug transport pathways [27].

NASAL DRUG DELIVERY SYSTEM (NDDS)

Nasal drug delivery systems (NDDS) have gained significant attention as an alternative to conventional routes due to their non-invasive nature and rapid onset of action. The nasal route enables

both local and systemic drug delivery, along with the potential for direct brain targeting via neuronal pathways [29]. The nasal route's rich blood supply enables rapid systemic absorption, and its direct brain connection via olfactory and trigeminal pathways makes it ideal for treating CNS conditions [30].

These systems are designed to enhance drug stability, improve permeability across the nasal mucosa, and prolong residence time at the site of absorption [31]. Recent advancements in NDDS have focused on improving drug stability, permeability, and retention within the nasal cavity. Various formulation strategies, including nanoparticle-based systems, nanoemulsions, liposomes, and polymeric gels, have been developed to enhance drug bioavailability and therapeutic effectiveness [32]. Different approaches involved in nasal drug delivery systems are represented in Figure 4.

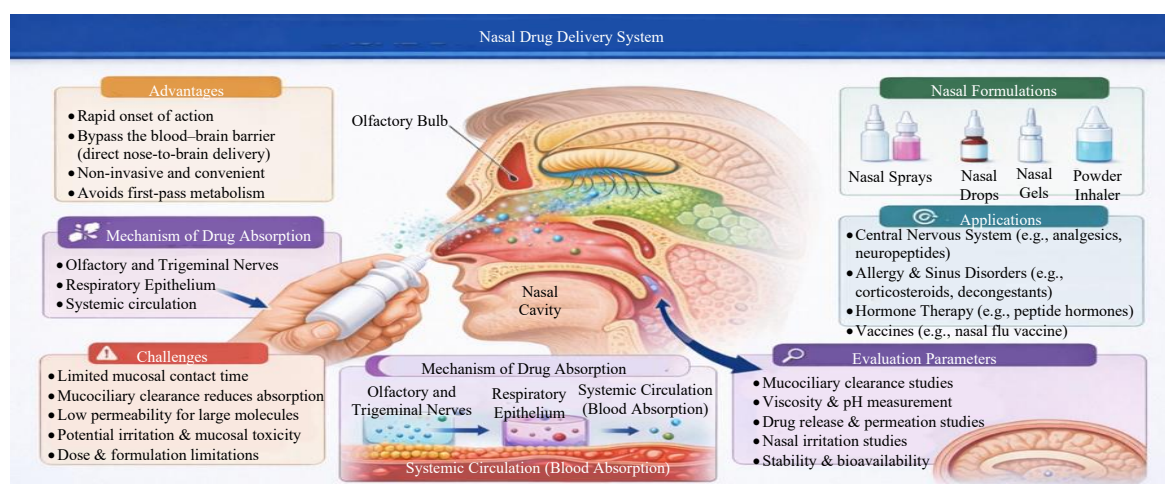


Figure 4. Nasal drug delivery system (NDDS) [33].

Advantages of NDDS

NDDS offers several advantages over traditional drug delivery routes:

- *Rapid Onset of Action:* Due to high vascularization, drugs are quickly absorbed into systemic circulation.
- *Avoidance of First-Pass Metabolism:* Drugs bypass hepatic metabolism, improving bioavailability.
- *Non-Invasive and Patient-Friendly:* Enhances patient compliance, especially in chronic conditions.
- *Direct Brain Targeting:* Enables drug delivery to the CNS via olfactory and trigeminal pathways.
- *Reduced systemic side effects:* Localized delivery minimizes unwanted systemic exposure [34].

Limitations of NDDS

Despite its advantages, NDDS also faces certain limitations:

- *Rapid Mucociliary Clearance:* Reduces residence time and drug absorption.
- *Limited Drug Dose Capacity:* Only small volumes can be administered intranasally.
- *Enzymatic Degradation:* Nasal enzymes may degrade certain drugs.
- *Irritation and Toxicity:* Some formulations may cause nasal irritation upon prolonged use.
- *Variability in Absorption:* Differences in nasal physiology among patients can affect drug delivery [35].

Challenges in Nasal Drug Delivery

The development of effective NDDS is associated with several challenges that must be addressed:

- *Short Residence Time:* Requires formulation strategies such as mucoadhesive systems [36].
- *Poor Permeability of Hydrophilic Drugs:* Necessitates the use of permeation enhancers or nanocarriers [37].

- *Stability Issues*: Especially for peptides and proteins [37].
- *Formulation Optimization*: Balancing viscosity, pH, and drug release characteristics is critical [38].

To overcome these challenges, advanced delivery systems – such as pH-triggered in-situ gels – have been developed, which can enhance drug retention and provide controlled release at the site of administration.

Types of Nasal Drug Delivery Systems

NDDS can be broadly classified into the following types:

Conventional Systems

- Nasal drops.
- Nasal sprays.
- Nasal solutions.

These systems are simple but suffer from poor retention and rapid clearance [39].

Novel Drug Delivery Systems

- *Mucoadhesive Systems*: These formulations use polymers that adhere to the nasal mucosa, thereby prolonging residence time and improving drug absorption [40].
- *Nanoparticle-Based Systems*: Nanocarriers – such as polymeric nanoparticles and lipid-based systems – enhance drug permeability and stability [41].
- *In-Situ Gel Systems*: These systems undergo sol-to-gel transformation upon administration, increasing viscosity and retention time in the nasal cavity [42].
- *Liposomal and Nanoemulsion Systems*: These improve drug solubility and protect drugs from degradation, especially useful for lipophilic and unstable drugs [43].

IN-SITU GEL DRUG DELIVERY SYSTEM

The in-situ gel system can be considered an innovation in drug development technology, where a sol-to-gel transition occurs after administration and increases retention and absorption. This approach has demonstrated significant potential for intranasal drug delivery by improving retention and bioavailability [44].

Principle and Mechanism

In situ gel systems involve polymers that can change their state depending on environmental factors such as pH, temperature, and ions. These factors lead to polymer hydration, the formation of three-dimensional networks, and increased viscosity to form gels. The process extends retention, decreases mucociliary clearance, and increases bioavailability [45].

Classification of In Situ Gel System

pH-responsive systems include polymers, such as carbopol, which gel under the influence of the pH level (from 5.5 to 6.5) in the nose, ionizing and expanding.

- *Temperature-Dependent Gel*: Such gels undergo gelation at body temperature. Such polymers include poloxamers where they exist in sol form at ambient temperature while undergoing gelation at body temperature [46].
- *Ion - Dependent Gel*: Such gels are activated by ions found in nasal mucosa fluid, e.g., Ca^{2+} , Na^{+} ions. Polymers include gellan gum and sodium alginate [47]. Commonly used polymers in in-situ nasal gel systems are summarized in Table 1.

Table 1. Polymers used in in-situ nasal gel systems [48].

Polymer	Type	Function
Carbopol	pH-sensitive	Gel formation.
HPMC	Viscosity enhancer	Stability.

Polymers Used in In-Situ Gel Systems

Benefits of In-Situ Gels

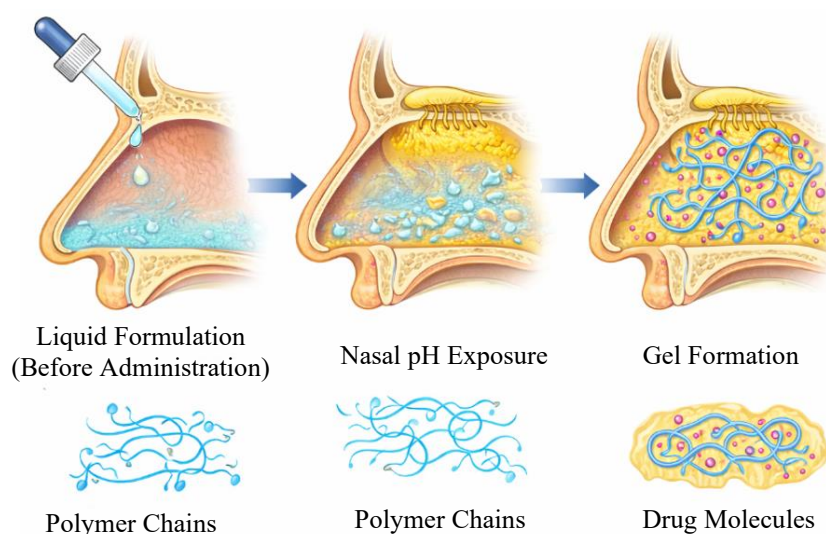
- *Increased Residence Time*: Minimizes drug losses caused by mucociliary transport.
- *Increased Bioavailability*: Increases drug absorption.
- *Drug Delivery Control*: Continuous therapeutic action.
- *Ease of Application*: Can be easily administered in liquid form.
- *Low Dosing Frequency*: Resulting from long-acting drugs [49].

Disadvantages of In-Situ Gels

- *Synthesis Difficulty*: Needs proper adjustment.
- *Nasal Irritation*: Caused by certain polymers.
- *Degradation*: Especially for natural polymers.
- *Gelation Inconsistency*: Batch-to-batch variation [50].

pH-RESPONSIVE IN-SITU GEL DELIVERY SYSTEMS FOR NASAL ADMINISTRATION

The pH-responsive in-situ gel delivery systems for nasal administration are considered sophisticated drug delivery systems that induce a transformation from a liquid to a gel state because of changes in the physiological pH of the nasal passages. The nasal in-situ gel system is usually prepared as a low-viscosity solution at acidic pH and transforms into a gel after nasal application because of an increase in pH [51]. The pH-induced sol-gel transformation mechanism of in-situ nasal gel is illustrated in Figure 5.



pH-Triggered sol-to-Gel Transition Mechanism of in-Situ Nasal Gel

Figure 5. pH-induced sol-gel transformation mechanism of in-situ nasal gel.

Gelation Process and Mechanism

The gelation process of pH-dependent gels depends upon the ionization reaction of the polymers sensitive to the pH change. The presence of polymers, such as Carbopol in lower pH, shows coiling effect, hence lower viscosity. On reaching pH of the nose cavity (5.5–6.5), ionization of carboxylic groups leads to polymer swelling and gel formation, producing repulsion forces among polymer molecules causing swelling and subsequent formation of a three-dimensional gel structure [52].

This change makes the gel formulation very viscous, hence useful in:

- Inhibiting mucociliary clearance.
- Mucoadhesion enhancement.

- Drug retention enhancement [53].

Polymers Used in pH-dependent Nasal Gels

Appropriate polymer selection is an important aspect when preparing an in-situ nasal gel for successful gelation and release of drugs [54].

Commonly used polymers in these gels include:

- *Carbopol (Carbomer)*: Highly efficient in gelling and exhibiting mucoadhesive properties [55].
- *Chitosan*: Biocompatible natural polymer with high permeability [56].
- *Polyacrylic Acid Derivatives*: Controlled release of drug through polymer gel [57].
- *Hydroxypropyl Methylcellulose (HPMC)*: Provides good viscosity and stabilization [58].

These polymers facilitate the development of stable gels, improved mucoadhesivity and sustained drug release.

Factors Influencing Gel Formation and Performance

Various formulation and physiologic factors play roles in the success rate of pH-dependent gels for in-situ nasal administration as follows:

- *Concentration of Polymer*: Affects viscosity and gel strength.
- *pH of Formulation*: Determines the efficiency of gelation.
- *Properties of Drugs*: Solubility and molecular weight affecting release.
- *Ionic Strength*: Affects behavior of polymers.
- *Viscosity*: Should be optimized for ease of administration.

All these should be well optimized for desired results [59, 60].

Advantages Compared to Conventional Nasal Delivery Systems

In comparison with conventional nasal formulations, pH-sensitive in situ gels have certain advantages that include:

- Longer residence time owing to the formation of a gel matrix.
- Promotion of bioavailability due to extended contact with mucosa.
- Sustained and controlled drug delivery.
- Frequency of dosing reduction.
- Patient compliance improvement.

The above-mentioned properties make in situ gels extremely valuable for the treatment of migraines [61, 62].

Application in Migraine Management

Migraine is a neurological condition which necessitates immediate drug effect for successful treatment of symptoms. Oral formulations generally exhibit delayed absorption properties and cause gastric complications. On the other hand, pH-sensitive in-situ gels in nasal administration allow for the direct delivery of drugs into the bloodstream as well as the brain, hence providing quick drug effect [63, 64].

Various studies have utilized sumatriptan and other triptans in nasal gels and shown positive results concerning bioavailability. Also, the capability of these systems in promoting nose-to-brain delivery provides further benefits for treating migraines using the CNS-targeted pathway [65, 66].

EVALUATION RESULTS OF PH-RESPONSIVE IN-SITU NASAL GEL FORMATION

Physical Appearance and Clarity

The prepared formulations are visually inspected for color, clarity, and presence of any particulate matter. An ideal nasal formulation should be clear, transparent, and free from visible impurities,

indicating uniform distribution of drug and excipients. Any turbidity or phase separation may indicate incompatibility or instability of the formulation [67, 63].

pH Measurement

The pH of the formulation is determined using a calibrated digital pH meter. It is important that the pH is maintained within the physiological range of the nasal cavity (approximately 5.5–6.5) to avoid irritation and ensure compatibility with nasal mucosa. Additionally, pH plays a crucial role in triggering gelation in pH-sensitive systems [68, 69].

Viscosity and Rheological Studies

Viscosity is measured using a suitable viscometer (e.g., Brookfield viscometer) at different shear rates. The formulation should exhibit low viscosity in the sol state to allow easy administration, followed by a significant increase in viscosity upon gelation. Rheological behavior is also studied to determine whether the formulation exhibits pseudoplastic or Newtonian flow, which influences spreadability and retention [70, 71].

Gelation Study

Gelation studies are performed to evaluate the ability of the formulation to undergo sol-to-gel transition when exposed to simulated nasal fluid. A small quantity of formulation is added to simulated nasal medium, and the time required for gel formation is observed. An ideal formulation should undergo rapid gelation and maintain gel integrity for a prolonged period [13, 72].

Mucoadhesive Strength

Mucoadhesive strength is assessed to determine the ability of the formulation to adhere to nasal mucosa. This parameter is critical for prolonging residence time and reducing mucociliary clearance. It is typically measured using a texture analyzer or modified balance method using excised nasal mucosal tissue [73, 74].

Drug Content Uniformity

Drug content is determined by analyzing a known quantity of formulation using appropriate analytical methods such as UV-visible spectrophotometry. Uniform drug distribution ensures dose accuracy and reproducibility across different batches [75, 76].

In-Vitro Drug Release Study

In-vitro drug release studies are carried out using diffusion systems such as Franz diffusion cells. The formulation is placed in the donor compartment, and the release medium is maintained under controlled conditions. Samples are withdrawn at predetermined intervals and analyzed to determine the drug release profile. Ideally, the formulation should provide sustained and controlled drug release [77, 78].

Ex-Vivo Permeation Study

Ex-vivo permeation studies are performed using excised nasal mucosa (e.g., sheep or goat nasal tissue) to evaluate drug permeation across biological membranes. This study provides insight into the formulation's ability to enhance drug absorption and predict in-vivo performance [79, 80].

Stability Studies

Stability studies are conducted according to ICH guidelines to assess the effect of storage conditions on formulation properties. Parameters, such as pH, viscosity, drug content, and physical appearance, are monitored over time. A stable formulation should show minimal variation in these parameters [81, 82].

Nasal Irritation Study

The safety of the formulation is evaluated by conducting nasal irritation studies, typically using animal models. Histopathological examination of nasal mucosa is performed to ensure that the

formulation does not cause any damage or inflammation to the tissue [83, 84]. The important evaluation parameters for pH-responsive nasal gels are summarized in Table 2.

Table 2. Evaluation parameters [85].

Parameter	Method	Purpose
pH	pH meter	Compatibility.
Viscosity	Brookfield	Flow behavior.
Gelation	SNF	Gel formation.
Release	Franz cell	Drug release.

RECENT ADVANCES IN pH-TRIGGERED IN-SITU NASAL GEL SYSTEMS

Recent years have witnessed significant progress in the development of pH-triggered in-situ nasal gel systems, particularly for enhancing drug delivery to the central nervous system (CNS). These advancements focus on improving drug bioavailability, targeting efficiency, and patient compliance through innovative formulation strategies and integration with nanotechnology [86].

Integration with Nanocarrier Systems

One of the major advancements in this field is the incorporation of nanocarriers such as nanoparticles, nanoemulsions, and nanostructured lipid carriers into pH-sensitive in-situ gels. These hybrid systems combine the advantages of both nanotechnology and gel-based delivery, resulting in improved drug solubility, stability, and permeation across nasal mucosa [87].

Recent studies have demonstrated that nanoparticle-loaded in-situ gels significantly enhance nose-to-brain drug transport and provide sustained drug release, making them highly effective for migraine and other CNS disorders [88].

Development of Multifunctional Polymers

Modern research has focused on the use of multifunctional polymers that exhibit both pH sensitivity and mucoadhesive properties. Polymers – such as modified carbopol and chitosan derivatives – have shown improved gel strength, enhanced adhesion, and better drug release profiles [89].

These polymers not only facilitate efficient gelation but also improve drug permeation by temporarily opening tight junctions in the nasal epithelium [90].

Targeted Nose-to-Brain Delivery

Advancements in nasal drug delivery have increasingly emphasized direct nose-to-brain targeting. pH-triggered in-situ gels are being optimized to enhance drug transport via olfactory and trigeminal pathways, thereby bypassing the blood–brain barrier [91].

This approach has shown promising results in the management of neurological disorders, such as migraine, Parkinson’s disease, and epilepsy, where rapid onset of action is critical [92].

Application in Migraine Therapy

Recent studies have explored the use of in-situ nasal gels for delivering antimigraine drugs such as sumatriptan and rizatriptan. These formulations have demonstrated:

- Faster onset of action.
- Improved bioavailability.
- Reduced systemic side effects.

The combination of pH-triggered gelation and mucoadhesion enhances drug retention in the nasal cavity, leading to improved therapeutic outcomes [93].

Use of Herbal and Natural Compounds

Emerging research has also focused on incorporating herbal drugs (e.g., plant extracts such as ginger) into nasal gel systems. These natural compounds exhibit anti-inflammatory and neuroprotective effects, making them suitable for migraine management [94].

Such formulations offer a safer alternative with reduced side effects compared to synthetic drugs [95].

Advanced Evaluation and Characterization Techniques

Recent advancements also include the use of sophisticated analytical techniques, such as:

- Texture profile analysis.
- In vivo imaging.
- Pharmacokinetic and pharmacodynamic studies.

These techniques provide deeper insights into the performance of in-situ gels and support their clinical translation [96].

Table 3. Analysis of recent studies.

Author	Year	Drug/active	Polymer/system	Key findings
Singh et al.	2025	CNS drug	Mucoadhesive gel	Improved retention.
Safarov et al.	2024	CNS drugs	In-situ nasal gel	Enhanced brain targeting.
Alshraim et al.	2024	Sumatriptan	Carbopol-based gel	Enhanced brain targeting.
Zhang et al.	2024	CNS drug	Nanocarrier gel	Improved targeting.
Patel et al.	2023	Rizatriptan	pH-triggered gel	Sustained drug release.
Mehta et al.	2023	Nanoparticle drug	Nano-gel system	Enhanced absorption.
Sharma et al.	2023	Nasal drug	Carbopol gel	Enhanced stability.
Nair et al.	2022	Various drugs	In-situ gel	Better permeation.
Kaur et al.	2022	Nasal drug	Carbopol + HPMC	Controlled release.
Bansal et al.	2022	Chitosan-based drug	Mucoadhesive gel	Increased permeability.
Mittal et al.	2022	Brain drug	In-situ gel	Rapid onset action.
Agrawal et al.	2022	Polymeric gel	In-situ system	Improved performance.
Ahmad et al.	2021	Herbal drug	Nasal gel	Reduced side effects.

Analysis of recent studies indicates that carbopol-based pH-responsive systems are widely preferred due to their superior gelation and mucoadhesive properties. Furthermore, the integration of nanocarriers into in-situ gels has significantly enhanced drug permeation and targeting efficiency. However, most studies are limited to in-vitro and ex-vivo evaluations, with fewer reports on clinical translation. This highlights the need for further in-vivo and clinical investigations to validate the therapeutic potential of these systems (Table 3) [97, 98].

RESEARCH GAP AND CRITICAL ANALYSIS

Despite significant progress in the development of intranasal drug delivery systems, several limitations and research gaps remain in the field of pH-triggered in-situ nasal gels, particularly for migraine therapy [99].

Firstly, most of the existing studies have primarily focused on synthetic drugs, such as triptans, while limited attention has been given to the incorporation of herbal therapeutic agents. Although natural compounds – like ginger extract and peppermint oil – exhibit promising anti-inflammatory and analgesic effects, their application in pH-responsive nasal gel systems remains insufficiently explored [100].

Secondly, most reported studies emphasize formulation development and in-vitro evaluation, with comparatively fewer investigations addressing ex-vivo, in-vivo, and clinical studies. This lack of clinical translation restricts the practical applicability of these systems in real-world therapeutic settings [101].

Furthermore, variability associated with herbal components, including differences in phytochemical composition and stability, presents additional challenges in achieving reproducible and standardized formulations. The absence of comprehensive comparative studies between conventional nasal formulations and advanced in-situ gel systems also limits the understanding of their relative therapeutic advantages [102].

In addition, although recent advancements have introduced nanocarrier-based in-situ gels, there is still a need for systematic evaluation of their long-term safety, toxicity, and regulatory acceptance. Issues related to large-scale manufacturing, stability during storage, and patient compliance also require further investigation [13].

Therefore, future research should focus on the integration of herbal therapeutics with advanced delivery systems, supported by robust in-vivo studies and clinical trials. Addressing these gaps will be essential for translating pH-triggered in-situ nasal gels from laboratory research to clinical application [24].

CONCLUSION AND FUTURE PERSPECTIVES

Conclusion

pH-triggered in-situ nasal gel systems represent a promising and advanced approach for drug delivery, particularly for targeting the central nervous system (CNS). These systems combine the advantages of both liquid and gel formulations, allowing easy administration followed by rapid gelation at physiological nasal pH. This transformation significantly enhances the residence time of the formulation within the nasal cavity, thereby improving drug absorption and bioavailability.

The incorporation of mucoadhesive and pH-sensitive polymers – such as carbopol and chitosan – has further strengthened the performance of these systems by promoting adhesion to nasal mucosa and enabling controlled drug release. Moreover, the ability of these formulations to facilitate direct nose-to-brain drug transport provides a major advantage in the treatment of neurological disorders, such as migraine, where rapid onset of action is essential.

Evaluation studies have demonstrated that pH-triggered in-situ gels exhibit desirable physicochemical properties, including optimal pH, appropriate viscosity, rapid gelation, strong mucoadhesion, and sustained drug release. These characteristics collectively contribute to improved therapeutic efficacy and patient compliance compared to conventional nasal dosage forms.

Future Perspectives

Despite significant advancements, further research is required to fully explore the potential of pH-triggered in-situ nasal gel systems. Future studies should focus on:

- *Advanced Polymer Development:* Designing novel polymers with enhanced responsiveness, biocompatibility, and controlled drug release properties.
- *Nanotechnology Integration:* Combining in-situ gels with nanocarriers – such as nanoparticles and lipid-based systems – to improve drug targeting and permeation efficiency.
- *Clinical and in Vivo Studies:* More extensive clinical trials are needed to establish the safety, efficacy, and long-term performance of these formulations.
- *Personalized Drug Delivery:* Development of patient-specific formulations based on disease condition and nasal physiology.

- *Exploration of Herbal Therapeutics:* Incorporation of natural compounds with therapeutic potential, such as plant-based extracts, for safer and more effective treatment options.
- *Regulatory and Commercialization Aspects:* Addressing scale-up challenges, stability issues, and regulatory requirements to facilitate successful translation from laboratory to market.

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