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Review Article

In Situ Mucoadhesive Nasal Gel Containing Anti-Migraine Drugs: A Comprehensive Review

Harshda Komarol*, Snehalata Mali, Gauri Bhamare, Muskan Malik, Pratik Londhe, Aditi Mane

Shivajirao. S. Jondhle College of Pharmacy, Thane, Maharashtra, 421601

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ABSTRACT

Migraine is a chronic, debilitating neurological condition characterised by recurrent episodes of severe headache often accompanied by nausea, vomiting, and sensory disturbances. Conventional oral drug administration for migraine is limited by gastrointestinal disturbances, hepatic first-pass metabolism, and delayed onset of action. In recent years, the nasal route has emerged as an attractive alternative for systemic drug delivery due to its rich vascularisation and rapid drug absorption. In situ mucoadhesive nasal gels, which transform from sol to gel upon exposure to nasal conditions, represent a promising strategy for targeted and sustained delivery of anti-migraine drugs. This review focuses on the development, characterisation, and therapeutic potential of in situ mucoadhesive nasal gels containing anti-migraine agents. It highlights the physiological and formulation aspects influencing nasal drug delivery, discusses various gelling mechanisms (temperature, pH, ionic), polymeric systems (chitosan, poloxamer, Carbopol), and evaluates preclinical and clinical outcomes. The integration of mucoadhesion and in situ gelling enhances residence time, drug absorption, and bioavailability while minimising systemic side effects. The review concludes by identifying key formulation challenges, regulatory considerations, and future directions in the optimisation of nasal in situ gel systems for migraine therapy.

INTRODUCTION

Migraine affects nearly 15–20% of the global population, predominantly among women, and represent one of the leading causes of disability worldwide according to the Global Burden of Disease Study (2021) [1]. It is characterised by unilateral pulsating headaches associated with nausea, photophobia, and phonophobia [2]. The pharmacotherapy of migraine includes triptans, ergot alkaloids, non-steroidal anti-inflammatory drugs (NSAIDs), and calcitonin generelated peptide (CGRP) antagonists [3].

***Corresponding Author:** Harshda Komarol
Address: *Shivajirao. S. Jondhle College of Pharmacy, Thane, Maharashtra, 421601*
Email : harshada.s.komarol2209@gmail.com
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Despite the availability of effective medications, oral administration—the most common route—faces challenges such as low bioavailability, delayed onset, and gastrointestinal intolerance [4]. Vomiting during attacks further reduces drug absorption [5]. To overcome these barriers, nasal drug delivery has gained attention as a non-invasive, rapid, and direct route to systemic circulation, bypassing hepatic first-pass metabolism [6].

However, nasal formulations like sprays and solutions suffer from rapid mucociliary clearance that limits drug retention time [7]. To address this, in situ mucoadhesive nasal gels have emerged as an innovative approach that combines mucoadhesion (for prolonged residence) with in situ gelation (for controlled release) [8]. These systems remain liquid at room temperature and form gels upon contact with the nasal mucosa, triggered by physiological stimuli such as temperature, pH, or ions [9].

This review explores the design, development, and evaluation of in situ mucoadhesive nasal gels specifically for anti-migraine drugs, aiming to provide a sustained, fast-acting, and patientfriendly dosage form.

2. Anatomy and Physiology of Nasal Cavity Relevant to Drug Delivery

The nasal cavity serves as a potential route for both local and systemic drug delivery due to its high vascularisation and large surface area (~150 cm^2) [10]. It is divided into three regions: vestibular, respiratory, and olfactory [11]. The respiratory region—lined with pseudostratified columnar epithelium—is the principal site for drug absorption [12].

Mucociliary Clearance

Mucus produced by goblet cells and serous glands entraps foreign particles and is cleared toward the nasopharynx within 15–20 minutes [13]. This rapid clearance can significantly limit the absorption of nasally administered drugs, which underscores the importance of mucoadhesive polymers in prolonging residence time [14].

Enzymatic Barrier

The nasal mucosa contains enzymes such as cytochrome P450, carboxylesterases, and peptidases, which can metabolise drugs before systemic absorption [15]. Formulation approaches such as enzyme inhibitors and protective polymers are used to enhance drug stability [16].

3. Rationale for Nasal Drug Delivery in Migraine Management

The nasal route offers multiple benefits over oral and parenteral routes in migraine therapy [17]:

- Bypass of hepatic metabolism, leading to higher bioavailability [18].
- Rapid absorption through the rich vasculature of the nasal mucosa [19].
- Avoidance of gastrointestinal irritation and ease of administration during nausea or vomiting [20].
- Direct access to the brain via olfactory and trigeminal pathways, offering potential for nose-to-brain delivery [21].

Drugs like sumatriptan, zolmitriptan, and rizatriptan have demonstrated faster onset and improved patient compliance when delivered intranasally compared to oral routes [22]

4. Concept of In Situ Gel Systems

In situ gel systems are polymeric formulations that undergo a sol-to-gel transition under physiological conditions [23]. This transformation may be

triggered by temperature, pH, or ionic concentration, allowing easy administration as a liquid and prolonged retention as a gel [24].

Mechanisms of Gelation

1. Thermoresponsive systems – Use polymers like Poloxamer 407, which form gels at body temperature (~35–37°C) [25].
2. pH-sensitive systems – Utilise polymers like Carbopol that gel at physiological pH (~6.2–6.5) [26].
3. Ion-activated systems – Employ gellan gum or alginate, which gel in the presence of cations such as Ca^{2+} and Na^{+} in nasal fluids [27].

Advantages

- Ease of administration as a liquid
- Prolonged contact due to gelation
- Controlled release profile
- Enhanced bioavailability [28]

5. Mucoadhesive Polymers

Mucoadhesion refers to the adhesion between a polymer and the mucus layer of the mucosa [29]. The mechanism involves wetting, diffusion, and chemical interactions (hydrogen bonding, ionic, and van der Waals forces) [30].

Common Mucoadhesive Polymers

Polymer	Mechanism	Examples in Nasal Gels
Chitosan	Ionic interaction with mucin	Sumatriptan [31]
Carbopol (polyacrylic acid)	Hydrogen bonding	Zolmitriptan [32]
HPMC / CMC	Swelling & diffusion	Rizatriptan [33]
Gellan gum	Ion-induced gelation	Eletriptan [34]
Pluronic F-127	Thermoresponsive	Naratriptan [35]

Ideal Characteristics

- Biocompatible and non-toxic
- Capable of adhering for 6–8 hours
- Should not interfere with ciliary function
- Must allow easy sol–gel transition [36]

6. Anti-Migraine Drugs Suitable for Nasal In Situ Gels

Migraine pharmacotherapy includes serotonin 5-$HT_1B/_1D$ agonists (triptans), ergot derivatives, and NSAIDs. Among these, triptans are the most explored for nasal delivery [37].

Sumatriptan

- First triptan approved for migraine [38].
- Oral bioavailability ~15% due to hepatic metabolism [39].
- Nasal gel formulations achieved a 2.5-fold increase in bioavailability [40].

Zolmitriptan

- Higher lipophilicity allows better brain penetration [41].
- Mucoadhesive in situ gels showed sustained release for up to 8 hours [42]

Rizatriptan

- High first-pass metabolism limits oral efficacy [43].
- Nasal in situ gel improved plasma concentration within 20 min [44].

Ele triptan & Naratriptan

- Both show improved therapeutic response with nasal gels compared to sprays [45,46].

7. Formulation and Evaluation Parameters

Formulation Components

- Gelling agent: Poloxamer 407 (15–20%) or gellan gum (0.5–1%)
- Mucoadhesive polymer: Chitosan, Carbopol 934P
- pH modifiers: HCl or NaOH to maintain nasal pH (5.5–6.5)
- Stabilisers & preservatives: Benzalkonium chloride, EDTA [47].

Evaluation Tests

Parameter	Method	Significance
Gelation temperature	Tube inversion method	Ensures gel forms at 33–37°C [48]
Viscosity	Brookfield viscometer	Indicates flow & retention [49]
Mucoadhesive strength	Texture analyser / shear stress	Determines adhesion with mucin [50]
In vitro drug release	Franz diffusion cell	Assesses release kinetics [51]
Ex vivo permeation	Porcine nasal mucosa	Estimates absorption potential [52]
Histopathological studies	Microscopy	Evaluates mucosal safety [53]

8. Pharmacokinetics and Drug Absorption

Nasal in situ gels facilitate rapid systemic absorption due to high vascularity and permeability [54]. For instance, sumatriptan nasal gel demonstrated a Cmax of 48 ng/mL within 15 min, significantly higher than oral formulations [55]. Moreover, the area under the curve (AUC) values indicated enhanced bioavailability up to 3 times compared to the oral route [56].

Mucoadhesion prolongs residence time, while controlled gelation maintains sustained release—together optimising pharmacokinetic parameters [57].

9. Clinical Studies and Applications

Clinical evaluations of nasal triptan gels have shown improved therapeutic efficacy and patient compliance [58]. A randomised crossover trial comparing sumatriptan nasal gel vs. oral tablets reported faster pain relief (mean onset: 15 min vs. 45 min) and fewer recurrences [59].

Additionally, zolmitriptan in situ gels showed a sustained plasma concentration and reduced headache recurrence [60]. No significant nasal irritation or toxicity was reported in most studies [61].

10. Advantages and Challenges

Advantages

- Non-invasive and user-friendly administration [62]
- Rapid onset and enhanced bioavailability [63]
- Prolonged residence via mucoadhesion [64]
- Potential for nose-to-brain delivery [65]

Challenges

- Limited drug loading capacity [66]
- Nasal irritation due to excipients [67]
- Variability in nasal physiology among patients [68]
- Regulatory complexities in approval [69]

11. Future Perspectives

Recent innovations such as nano-in-gel systems, thermo-mucoadhesive nanoparticles, and CGRP-targeted nasal formulations have demonstrated enhanced targeting efficiency [70–72]. The combination of nanocarriers with in situ gels can

improve brain bioavailability and reduce systemic side effects [73]

Advances in 3D printing, bio-responsive polymers, and AI-based formulation design are expected to revolutionise personalised nasal migraine therapy [74–76].

CONCLUSION

In situ mucoadhesive nasal gels represent a novel, effective, and patient-centric approach for migraine management. By combining mucoadhesion and stimuli-responsive gelation, these systems overcome limitations of conventional oral and parenteral therapies. Enhanced residence time, rapid absorption, and sustained release contribute to superior therapeutic outcomes. Future research should focus on clinical translation, long-term safety, and scalability of such formulations for broader clinical use.

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