Available online on 15.04.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

Nasal In situ Gel Systems for Enhanced Drug Delivery: A Comprehensive Review

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A B S T R A C T

Intranasal delivery has emerged as a promising alternative route for drug administration due to its non-invasive nature, rapid absorption, and ability to bypass hepatic first-pass metabolism. In recent years, nasal in-situ gel systems have gained considerable interest as they offer improved retention time and controlled drug release within the nasal cavity. These systems are designed to be administered as low-viscosity liquids that convert into gels upon contact with physiological conditions such as temperature, pH changes, or ions present in nasal secretions. This sol-to-gel transition enhances mucoadhesion, minimizes the chances of formulation drainage, and ensures prolonged interaction of the drug with the nasal mucosa, thereby increasing therapeutic efficiency.

Different polymers such as Poloxamers, Carbopol, Gellan gum, and Sodium alginate are widely used in these formulations due to their stimuli-responsive gelling properties and biocompatibility. The ideal nasal in-situ gel should possess optimal viscosity for easy administration, suitable gel strength for retention, and must maintain clarity, stability, sterility, and uniform drug content. Such formulations have demonstrated significant potential in delivering a broad range of therapeutic agents including analgesics, anti-inflammatory drugs, peptides, vaccines, and central nervous system (CNS) active compounds, especially where rapid and sustained action is desired.

Evaluation of nasal in-situ gels involves assessing parameters like gelling capacity, viscosity, gel strength, drug release behavior, isotonicity, sterility, and stability studies to ensure safety and effectiveness. Overall, nasal in-situ gel technology offers a versatile and patient-friendly platform capable of improving drug bioavailability and enhancing clinical outcomes for various therapeutic applications.

KEYWORDS: Nasal drug delivery, In-situ gel, Thermosensitive polymers, pH-triggered gelation, Ion-activated gelation.

A R T I C L E I N F O: Received 12 Dec. 2025; Review Complete 13 Feb. 2025; Accepted 02 March 2026; Available online 15 April. 2026

Cite this article as:
Ashwin PA, Bobade N N, Pande SD, Atram S C, Wankhade V P,Nasal In situ Gel Systems For Enhanced Drug Delivery : A Comprehensive Review, Asian Journal of Pharmaceutical Research and Development. 2026; 14(2):26-31,
DOI: http://dx.doi.org/10.22270/ajprd.v14i2.1715

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INTRODUCTION

The nasal route has emerged as an important pathway for drug delivery, with an increasing number of formulations designed for both local and systemic use.[1] Among the innovative dosage forms, in-situ gels have gained particular attention in recent years. Unlike conventional nasal liquids, in-situ gels are administered as low-viscosity solutions that transform into gels upon contact with the nasal mucosa. This sol-to-gel transition prolongs the residence time of the formulation, enhances drug absorption at the mucosal surface, and enables controlled release within the nasal cavity.[2]

A gel is essentially an intermediate state between liquid and solid, formed by a three-dimensional network of polymers that entraps liquid molecules within. Before administration, an in-situ gelling system exists as a simple aqueous solution. Once exposed to physiological conditions, it undergoes gelation, providing sustained and reproducible drug release. These systems are valued for their biocompatibility, stability, and dosing accuracy, which makes them attractive for therapeutic applications.[3-4]

In-situ gels can be formulated for multiple routes of administration, including oral, ocular, vaginal, rectal, intravenous, and intraperitoneal delivery. Gelation is

typically driven by polymer cross-linking, achieved either through covalent (chemical) bonds or non-covalent (physical) interactions. Depending on the formulation, gel formation can be triggered by physiological stimuli (such as changes in temperature or pH), physical alterations in biomaterials (like solvent exchange or swelling), or chemical reactions (including ionic crosslinking or light activation). A notable advantage is that these formulations generally do not require organic solvents or co-polymerization agents, simplifying their development. Importantly, nasal in-situ gels bypass hepatic first-pass metabolism, making them particularly suitable for sensitive molecules like peptides and proteins, which are otherwise degraded in the gastrointestinal tract.[1,2]

Nasal Drug Delivery System

Intranasal delivery is now widely recognized as a practical and efficient approach for drug administration. It offers advantages for both local treatment and systemic absorption, and has even shown promise in targeting drugs to the central nervous system (CNS).

Local delivery: The nasal route is the natural choice for treating conditions confined to the nasal cavity. Drugs such as antihistamines and corticosteroids are routinely prescribed for rhinosinusitis, while decongestants are commonly used for colds and related disorders. In such cases, intranasal administration ensures rapid onset of action and fewer systemic side effects compared to oral alternatives.[5,6]

Systemic delivery: Beyond local action, the nasal cavity provides an effective alternative to oral and parenteral routes for systemic drug delivery. A growing range of therapeutic agents—including analgesics (e.g., morphine), cardiovascular drugs (e.g., propranolol, carvedilol), hormones (e.g., progesterone, levonorgestrel, insulin), anti-inflammatory agents (e.g., indomethacin, ketorolac), and antiviral drugs (e.g., acyclovir)—have been successfully delivered via this route. This highlights the potential of nasal formulations to improve patient compliance and expand therapeutic options.[7]

Overall, the combination of nasal delivery with in-situ gelling technology presents a promising platform for achieving targeted, sustained, and patient-friendly drug administration.[8]

Anatomy and Physiology of the Nose [9-12]

A clear understanding of nasal anatomy and physiology is crucial for designing effective intranasal drug delivery systems. The nasal cavity serves multiple functions, primarily respiration and olfaction, while also protecting the lower airways by filtering, warming, and humidifying inspired air. In humans, the nasal cavity has a total volume of about 15–20 mL and a surface area of nearly 150 cm². It is divided into two chambers by the septum, with each side having a volume of approximately 7.5 mL and a surface area of about 75 cm². The pH of nasal secretions varies between 5.0–6.7 in children and 5.5–6.5 in adults. The nasal epithelium is coated with a mucus layer, which is continuously renewed every 10–15 minutes. Mucus clearance occurs at a rate of around 5–6 mm per minute, allowing foreign particles to be eliminated within 20 minutes.

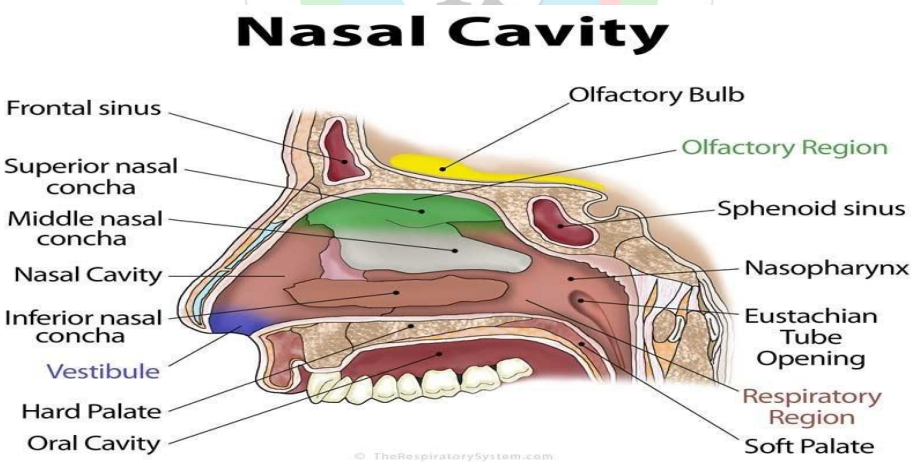

Figure 1: Anatomy and physiology of Nose

Structurally, the nasal cavity can be divided into three major regions:

1. **Respiratory Region:**

   The respiratory area, also referred to as the conchae, constitutes the largest section of the nasal cavity and is the primary site for systemic drug absorption. This region contains three turbinates—superior, middle, and inferior—projecting from the lateral wall of each cavity. The respiratory epithelium consists of four main cell types: ciliated columnar cells, non-ciliated columnar cells, goblet cells, and basal cells. Owing to its rich vascularization and relatively large surface area, this region is considered the most significant for nasal drug delivery.

2. **Vestibular Region:**

   Located at the anterior end of the nasal cavity, the vestibule is the first site of contact for inhaled air. It covers an area of about 0.6 cm² and is lined with stratified squamous epithelium containing keratinized cells and sebaceous glands. Its main role is to trap and filter airborne particles, making it less relevant for drug absorption.

3. Olfactory Region:

Found in the roof of the nasal cavity, the olfactory region extends slightly along the septum and lateral wall, with a surface area of roughly 10 cm^2. Despite its smaller size, it plays a critical role in drug transport to the central nervous system (CNS). Drugs administered intranasally can reach the brain through three potential pathways:

Systemic circulation pathway: Drugs absorbed through the nasal mucosa enter the bloodstream and subsequently cross the blood–brain barrier (BBB), particularly in the case of lipophilic molecules.

Olfactory pathway: Drugs may directly access the brain via the olfactory epithelium, either through intracellular axonal transport to the olfactory bulb or via transcellular and paracellular routes across sustentacular cells.

Trigeminal neural pathway: Drugs can also reach the brain and cerebrospinal fluid (CSF) through the trigeminal nerve branches that innervate the nasal cavity.

These unique anatomical and physiological features make the nasal route an attractive option, not only for local and systemic therapy but also for direct nose-to-brain drug delivery.

Advantages of Nasal Drug Delivery [13-15]

- Provides rapid absorption of drugs into systemic circulation.
- Non-invasive route, eliminating the need for injections.
- Simple and convenient method of administration.
- Ensures better bioavailability for many therapeutic agents.
- Enhances patient compliance due to ease of use and comfort.
- The nasal mucosa offers a large surface area for efficient absorption.
- Produces a quick onset of action.
- Generally associated with fewer systemic side effects.
- Suitable for drugs that are unstable or poorly absorbed through the oral route.
- Enables certain drugs to bypass the blood–brain barrier.
- Avoids first-pass metabolism, improving overall drug efficiency.

Disadvantages of Nasal Drug Delivery [13-15]

- Once administered, drug removal from the nasal cavity is difficult.
- Limited range of drugs can be effectively delivered through this route.
- Irritating or sensitizing compounds cannot be administered nasally.
- The dose volume is restricted to approximately 25–200 µL per administration.
- Only drugs with low molecular weight are suitable for nasal absorption.
- Frequent administration may cause nasal mucosal irritation or damage.
- Allergic reactions may occur in sensitive individual
- Drug distribution may be inconsistent, leading to variable absorption across different nasal regions or in the brain.

IN-SITU GEL FORMULATION [16,17]

Several mechanisms are employed in the formulation of in-situ gels, which are discussed below:

A. Stimuli-Responsive In-Situ Gelling Systems

1. Thermally Triggered Systems (Temperature):

In this mechanism, gel formation occurs due to temperature changes. Certain polymers undergo a sol-to-gel transition when exposed to physiological body temperature. As the temperature rises, these polymers transform from a liquid (sol) state into a semi-solid (gel) form, resulting in the formation of an in-situ gel at the site of administration.

2. pH-Triggered Systems:

This system relies on pH changes within the body to induce gelation. Polymers that are sensitive to pH variations are used in such formulations. For instance, hydrogels containing weakly acidic groups swell more as the external pH increases, while those with weakly basic groups exhibit reduced swelling at higher pH levels. Thus, the physiological pH acts as the trigger for gel formation.

3. Osmotically Induced In-Situ Gelling Systems:

In this type, gelation occurs due to alterations in the ionic strength of the surrounding environment. The rate of gel formation is influenced by the osmotic gradient across the gel surface. When the polymer solution encounters mono- or divalent cations, it transitions into a clear gel. Common polymers that undergo ion-induced gelation include gellan gum, alginic acid, and hyaluronic acid.

B. Chemically Induced In-Situ Gel Systems

a. Ionic Cross-Linking

Certain ion-sensitive polysaccharides such as carrageenan, gellan gum, pectin, and sodium alginate undergo gelation through ionic interactions. These polymers respond to the presence of ions like potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), and sodium (Na^+), resulting in the formation of a stable gel network through cross-linking mechanisms.

b. Enzymatic Cross-Linking In-Situ Systems

Gel formation through enzymatic catalysis is a relatively less explored approach; however, it offers notable advantages compared to chemical or photochemical methods. This technique utilizes natural enzymes to initiate gelation under mild physiological conditions, eliminating the need for toxic agents such as synthetic monomers or chemical initiators. As a result, enzymatic cross-linking provides a safer and biocompatible alternative for in-situ gel formation.

MANUFACTURING METHODS [18-23]

The formulation of nasal in-situ gels can be broadly classified according to the stimulus that induces the sol–gel transition. These stimuli-based systems employ distinct polymers and preparation strategies, which include **the cold method, pH-triggered approach, and ion-activated method.**

1. Cold Method (Thermosensitive Systems)

Principle:

Thermosensitive polymers such as Poloxamers (Pluronic® F127, F68) exhibit a reversible sol–gel transition depending on temperature. At low temperatures (below 10 °C), they remain as free-flowing liquids, while at physiological temperatures (around 32–34 °C), they form a semi-solid gel due to micelle aggregation and packing.

Method:

- The required quantity of Poloxamer is gradually added to chilled distilled water (4–5 °C) under continuous agitation to prevent clump formation.
- The dispersion is refrigerated for 12–24 hours to enable complete hydration of the polymer.
- The active pharmaceutical ingredient and other excipients such as stabilizers, mucoadhesive agents, and preservatives are incorporated into the hydrated polymer solution.
- The resulting formulation remains in a liquid form at storage temperature but converts into a gel upon intranasal administration.

Applications:

This approach is extensively used for the controlled nasal delivery of biomolecules such as peptides, proteins, anti-inflammatory, and CNS-targeted drugs.

2. pH-Triggered Method (pH-Sensitive Systems)

Principle:

pH-sensitive polymers such as Carbopol (polyacrylic acid) remain in solution at low (acidic) pH but undergo gelation as the pH increases toward the nasal physiological range (4.5–6.5). This gelation is attributed to ionization of the carboxyl groups, resulting in electrostatic repulsion and expansion of polymer chains.

Method:

- Carbopol is dispersed in purified water under continuous stirring while maintaining an acidic pH to ensure solubility.
- Secondary polymers like HPMC or chitosan can be incorporated to enhance the gel's strength and mucoadhesive characteristics.
- The drug is either dissolved or uniformly suspended in the polymeric dispersion.
- The pH is maintained around 4.0 so that the formulation remains liquid during storage.
- Once administered intranasally, the formulation encounters nasal pH, triggering gel formation in situ.

Applications:

pH-triggered gels are beneficial for formulations requiring prolonged nasal residence and for delivering pH-sensitive or peptide-based drugs.

3. Ion-Activated Method (Ion-Sensitive Systems)

Principle:

Certain natural polysaccharides, such as Gellan gum, Sodium alginate, and Pectin, possess ion-sensitive characteristics and form gels upon contact with cations (Na^+, K^+, Ca^{2+}) present in nasal secretions. Gelation results from ionic cross-linking among polymer chains.

Method:

- The polymer is dissolved in deionized water with gentle stirring until a clear solution forms.
- The drug and auxiliary excipients (e.g., mucoadhesive polymers, stabilizers, preservatives) are then incorporated.
- The system remains in sol form in the absence of ions.
- Upon contact with nasal mucosal ions, the formulation undergoes sol–gel transformation via ionic cross-linking.

Applications:

Ion-activated systems are commonly utilized for sustained nasal drug release, especially for hydrophilic macromolecules and vaccines.

Evaluation Parameters of Nasal In-Situ Gels [24-32]

1. Clarity

The transparency of the formulation can be examined visually against both black and white backgrounds to ensure the absence of any particulate matter or turbidity.

2. Viscosity

The viscosity and rheological behavior of the polymeric systems, either in solution or after gelation in simulated tissue fluid, can be determined using viscometers such as the Brookfield or cone and plate viscometer. The viscosity should be optimized to ensure ease of administration and patient compliance.

3. Texture Analysis

The firmness, cohesiveness, and consistency of the in-situ gel are analyzed using a texture analyzer. These parameters indicate the syringeability and ease of administration of the sol form, ensuring smooth in-vivo application.

4. Drug Content

One milliliter of the formulation is taken and diluted to 10 ml with distilled water in a volumetric flask. From this, 1 ml is again diluted to 10 ml. The absorbance of the final solution is measured using a UV–Visible spectrophotometer at the drug's specific wavelength to determine drug content uniformity.

5. Gel Strength

Gel strength can be evaluated with a rheometer. A specific volume of the sol is allowed to form a gel in a beaker, through which a probe is allowed to pass slowly. The force required to penetrate the gel is measured as a function of probe immersion depth, indicating the strength of the gel network.

6. Sol–Gel Transition Temperature and Gelling Time

For thermo-responsive systems, the temperature and time required for sol-to-gel transformation are measured. Gelling time is defined as the duration needed for the initial appearance of gelation, while the transition temperature should ideally match physiological conditions.

7. Drug–Polymer Interaction and Thermal Analysis

Drug–polymer compatibility is assessed using Fourier Transform Infrared (FTIR) spectroscopy with the KBr pellet method to identify any chemical interactions. Thermal behavior is examined through Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) to determine moisture content and thermal stability compared to pure drug samples.

8. Gelling Capacity

The in-situ gel's gelling ability can be evaluated by mixing it with simulated nasal fluid in a ratio of 25:7 (application volume: nasal fluid). Gelation is visually assessed based on the time required for gel formation and its subsequent dissolution behavior.

Figure 2: Mechanism of determination of gel strength

Figure 3: Measurement of gelling capacity

9. Isotonicity Evaluation

Isotonicity ensures that the formulation does not cause irritation or damage to nasal mucosa. The test involves mixing the formulation with a few drops of blood and examining it microscopically (45× magnification) for any morphological changes in red blood cells, comparing the results with those from a standard marketed formulation.

10. Sterility Testing

Sterility testing is performed in accordance with Indian Pharmacopoeia (IP, 1996). The samples are incubated for at least 14 days — at 30–35°C in Fluid Thioglycollate Medium to detect bacterial growth and at 20–25°C in Soybean Casein Digest Medium to identify fungal contamination.

11. Accelerated Stability Studies

The formulations are stored in amber-colored, sealed vials and subjected to accelerated stability conditions (40°C ± 2°C and 75% ± 5% RH) as per ICH guidelines to evaluate physical stability, drug content retention, and overall formulation integrity.

12. In-Vitro Drug Release Studies

The release behavior of in-situ gels can be assessed using a dialysis membrane method. The sol form is placed in the donor compartment of a two-chambered diffusion cell separated by a cellulose membrane. The receptor compartment contains release medium maintained at physiological temperature and oscillation rate. Samples are withdrawn at specific time intervals, replaced with fresh medium, and analyzed spectrophotometrically to determine drug release kinetics.

CONCLUSION

Nasal in-situ gel technology represents a promising alternative to conventional nasal formulations. By combining the ease of nasal administration with extended retention and controlled release behavior, these systems can improve therapeutic effectiveness and patient comfort. The ability of in-situ gels to enhance drug absorption and, in some cases, support nose-to-brain delivery offers significant advantages, particularly for drugs that face challenges in oral or injectable routes. However, further optimization in polymer selection, gelation characteristics, and long-term stability is still needed before wider clinical use. Overall, nasal in-situ gels hold strong potential for the future of patient-friendly and efficient drug delivery.

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