*EJPMR, 2026, 13(5), 103-107* **Review Article** **Impact Factor: 8.158**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

**ISSN (O): 2394-3211**
**ISSN (P): 3051-2573**
**Coden USA: EJPMAG**

# A COMPREHENSIVE REVIEW ON FORMULATION AND EVALUATION OF NASAL SPRAY IN-SITU GEL FOR SYSTEMIC AND LOCAL DRUG DELIVERY

**Arun B. M.*[1], Ganesh Raghunath Nayak[2], A. R. Shabaraya[3]**

[1,2,3]Srinivas College of Pharmacy, Valachil, Farangipete, Mangalore – 574143, Karnataka, India.

***Corresponding Author: Arun B. M.**

Srinivas College of Pharmacy, Valachil, Farangipete, Mangalore - 574143, Karnataka, India.

**DOI:** https://doi.org/10.5281/zenodo.19884010

**How to cite this Article:** Arun B. M.*[1], Ganesh Raghunath Nayak[2], A. R. Shabaraya[3]. (2026). A Comprehensive Review on Formulation and Evaluation of Nasal Spray In-Situ Gel For Systemic And Local Drug Delivery. European Journal of Pharmaceutical and Medical Research, 13(5), 103–107.



**Article Received on 27/03/2026** **Article Revised on 16/04/2026** **Article Published on 01/05/2026**

## ABSTRACT

Nasal drug delivery offers significant advantages due to the nasal cavity's high vascularization, large surface area, and ability to bypass first-pass metabolism. However, conventional nasal formulations such as drops and sprays are limited by rapid mucociliary clearance, which reduces residence time and bioavailability. Nasal spray in-situ gelling systems represent an innovative approach to overcome this limitation by undergoing sol-gel transition upon exposure to physiological conditions in the nasal cavity. These formulations are administered as low-viscosity solutions that transform into gels triggered by temperature, pH, or ionic composition of the nasal environment. This review comprehensively examines recent advancements in nasal spray in-situ gels for both local and systemic drug delivery. Key polymers including thermoreversible agents (Poloxamer 407/188), pH-sensitive polymers (Carbopol), and ion-sensitive polymers (gellan gum, alginate) are discussed, along with essential formulation components such as mucoadhesive polymers, permeation enhancers, and preservatives. The review elaborates on formulation strategies tailored for local applications (e.g., corticosteroids for allergic rhinitis) and systemic delivery (e.g., peptides, proteins, and small molecules). Critical evaluation parameters including physicochemical characterization, spray characteristics, in vitro drug release, ex vivo permeation, mucoadhesive strength, and in vivo pharmacokinetic and pharmacodynamic studies are detailed. Despite challenges related to device compatibility, mucosal irritancy, dose volume limitations, and scale-up complexities, ongoing research into novel polymers, combination trigger systems, nanocarrier-loaded gels, and nose-to-brain delivery pathways demonstrates immense potential. Nasal spray in-situ gelling systems emerge as a promising platform that combines precise dosing of spray devices with prolonged retention and sustained release, offering enhanced bioavailability and patient compliance for a wide range of therapeutic applications.

**KEYWORDS**: Nasal drug delivery; in-situ gel; mucociliary clearance; sol-gel transition; thermoreversible polymers, systemic delivery; local delivery; bioavailability; sustained release; permeation enhancers; nose-to-brain delivery.

## 1. INTRODUCTION

The nasal route, with its highly vascularized, large surface area, and porous endothelial lining, is a favorable route for drug delivery.[1] It provides a non-invasive method for systemic drug delivery, especially for poorly orally absorbed drugs such as peptides and proteins, thereby bypassing first-pass effects and gastrointestinal tract degradation.[2] Moreover, it is the route of choice for the treatment of local diseases such as allergic rhinitis, congestion, and infections.[3]

However, the conventional nasal preparations (drops and sprays) have one major drawback: rapid mucociliary clearance.[4] The clearance of the nasal cavity is usually achieved within 15-20 minutes, thus limiting the absorption time.[5] This results in poor bioavailability, thus requiring frequent administration. To overcome this problem, mucoadhesive and in situ gelling systems have been investigated.[6]

In situ gelling systems are intelligent polymeric systems designed to be delivered as low-viscosity solutions that

change to a gel upon contact with the nasal cavity's physiological conditions.[7] When combined with the accuracy of a nasal spray delivery system, they offer precise dosing and improved patient compliance with increased residence time and sustained release of the drug.[8] This review article summarizes recent developments in the formulation, testing, and use of nasal spray-in-situ gels for systemic and local drug delivery.[9]

## 2. Advantages of Nasal In-Situ Gelling Sprays

The combination of spray technology and in situ gelation provides a number of complementary advantages.[10]

**Increased residence time**: The resulting gel remains on the nasal mucosa, resisting mucociliary transport and allowing sustained drug release.[7]

**Improved bioavailability**: The longer contact time with the absorption surface allows better drug diffusion and increased systemic bioavailability.[8]

**Patient compliance**: The spray formulation is easy to use, painless, and does not require the patient to lie down or tilt their head backward as far as the nasal drops formulation.[11]

**Less frequent dosing**: The sustained-release system can significantly reduce the dosing interval, thereby improving patient compliance.[12]

**Stabilization of labile drugs**: The gel system provides protection for labile drugs, such as proteins and peptides, from enzymatic degradation in the nasal environment.[13]

## 3. Mechanisms of In Situ Gelation

The sol-gel transition in the nasal environment is triggered by one or a combination of three major physiological stimuli.[14]

### 3.1. Temperature-Induced Gelation (Thermoreversible)

Polymers such as Poloxamer 407 (Pluronic F-127) and Poloxamer 188 are mainly used for this purpose.[15] These polymers are low-viscosity solutions at room temperature (20-25°C) but transform into gels at physiological temperatures (34-37°C).[16] The gelation process is caused by the dehydration and subsequent entanglement of polymer chains due to the temperature increase.[14] The concentration of the polymer is crucial, as the gelation temperature should be lower than the temperature of the nasal cavity to allow instantaneous gelation.[17]

### 3.2. pH-Induced Gelation

Some polymers, like Carbopol (polyacrylic acid derivatives), are liquid at low pH but form a gel when the pH is increased towards the physiological pH of the nasal passage (5.0-6.5).[18] The Carbopol polymer chains expand with increasing pH due to the ionization of carboxyl groups, forming a three-dimensional network structure of the gel.[19]

### 3.3. Ion-Induced Gelation

Polymers such as sodium alginate and gellan gum (Gelrite) form a gel in the presence of specific ions.[20] The nasal fluid contains cations such as $Na^+$, $K^+$, and $Ca^{2+}$.[21] When these ions come into contact with the polymer, cross-linking of the polymer chains occurs, forming a gel.[22] For example, gellan gum forms a strong gel in the presence of mono- and divalent cations.[23]

| Polymer Type | Trigger | Examples | Key Benefit |
|---|---|---|---|
| Thermoreversible | Temperature | Poloxamer 407, 188 | Instant gel at 34-37°C |
| pH-Induced | pH (5-6.5) | Carbopol | Ionization forms network |
| Ion-Induced | Cations | Gellan gum, alginate | Cross-linking in nasal fluid |

## 4. Formulation Components

A nasal in situ gel spray formulation typically consists of several key components[24]:

**Drug**: Suitable for local use (antihistamines, corticosteroids, decongestants) or systemic use (antiemetics, cardiovascular drugs, hormones, analgesics, peptides).[9]

**Gelling Polymers:** The main component, usually used in a combination to provide the desired gelation temperature and mucoadhesive properties (Poloxamer 407 and Carbopol or HPMC).[17]

**Mucoadhesive Polymers:** Chitosan, hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (Na-CMC), and polycarbophil are used to improve adhesion to the mucus layer.[25]

**Permeation Enhancers:** More important in systemic delivery of macromolecules.[26] Common permeation enhancers include chitosan (which also modulates tight junctions), cyclodextrins, bile salts (sodium taurocholate), and fatty acids.[27]

**Solvents and Vehicles**: Purified water is the main solvent. Buffers (phosphate buffer, citrate buffer) are used to provide pH and stability.[28] Preservatives (benzalkonium chloride, EDTA) are added to prevent microbial growth in multi-dose preparations.[29]

## 5. FORMULATION STRATEGIES FOR SPECIFIC DELIVERY

### 5.1. For Local Drug Delivery

The goal here is to maximize drug concentration at the site of action within the nasal cavity while minimizing systemic absorption.[30] Formulations focus on high mucoadhesion and sustained release.[31] Examples include in situ gels for corticosteroids (e.g., fluticasone propionate) for allergic rhinitis and antihistamines (e.g., azelastine).[32] The gel matrix holds the drug on the mucosa, providing prolonged therapeutic effect.[25]

### 5.2. For Systemic Drug Delivery

The objective is to facilitate drug absorption into the systemic circulation.[33] Formulations are designed for sustained release and enhanced permeation.[34]

**Peptides and Proteins**: Insulin is the most widely studied model drug.[35] Various studies have demonstrated that insulin-loaded in-situ gels, particularly those containing permeation enhancers like chitosan or bile salts, can achieve significant hypoglycemic effects in animal models, with higher bioavailability compared to simple solutions.[20]

**Small Molecule Drugs:** Drugs with poor oral bioavailability, such as antiemetics (ondansetron, granisetron), cardiovascular drugs (carvedilol, propranolol), and hormones (progesterone), have been successfully formulated into in situ gels to bypass first-pass metabolism and achieve rapid systemic absorption.[11]

## 6. Evaluation of Nasal Spray In-Situ Gels

A full set of tests is necessary to assess the quality, safety, and performance of these formulations.[10]

### 6.1. Physicochemical Characterization

**Visual Appearance and Clarity**: The formulation should be clear and free from particulate matter.[28]

**pH:** Should be compatible with the nasal mucosa (4.5–6.5) to minimize irritation.[2]

**Drug Content:** Uniform drug content is essential for dose accuracy.[13]

**Viscosity and Rheological Behavior:** Measurements are conducted at storage (25°C) and physiological (34°C) temperatures.[4] A marked increase in viscosity at body temperature indicates gelation. Rheological tests also determine the strength and spreadability of the gel.[16]

**Gelation Temperature and Time:** The temperature at which gelation occurs and the time required for gelation at that temperature are critical parameters, usually determined by the test-tube inverting method or rheometry.[15]

### 6.2. Spray Characteristics

**Droplet Size Distribution:** Determined by laser diffraction. For nasal deposition, the optimal droplet size generally ranges between 10-100µm.[22] Smaller droplets may reach the lungs, whereas larger droplets may drip out.[33]

**Spray Pattern and Plume Geometry:** These tests define the spray shape and angle, which affect deposition in the nasal cavity.[29] They are usually performed using spray-view instruments.[24]

**Dose Uniformity per Spray:** Essential for ensuring that each spray delivers a uniform dose.[8]

### 6.3. In Vitro Drug Release

Performed using diffusion cells (Franz diffusion cell) with a synthetic membrane.[12] The formulation is placed in the donor compartment, and the release of drug into the receptor medium is measured over time.[18] This method helps in understanding the release kinetics (e.g., Higuchi, zero-order, Korsmeyer-Peppas models).[21]

### 6.4. Ex Vivo Permeation and Mucoadhesion

Permeation Studies: Conducted using excised nasal mucosa (commonly taken from sheep, goat, or rabbit) in a Franz diffusion cell. This approach helps assess the permeability of the drug through the biological membrane, providing a more realistic estimate of absorption.

**Mucoadhesive Strength:** Measured by calculating the force required to remove the gel from a model membrane or excised mucosa, often using a texture analyzer. Mucoadhesive strength is directly proportional to residence time.

### 6.5. In Vivo Studies

**Animal Models**: Rats and rabbits are generally used.[31] For systemically administered drugs, pharmacokinetic parameters (Cmax, Tmax, AUC, bioavailability) are calculated from plasma concentrations of the drug.[34] For locally administered drugs, pharmacodynamic parameters are evaluated.[32]

**Nasal Ciliotoxicity Studies:** Histopathological analysis of the nasal mucosa after repeated dosing is necessary for evaluating the safety and biocompatibility of the formulation and its components.[5]

**Gamma Scintigraphy:** This method allows direct visualization of the deposition, distribution, and clearance of the radiolabeled formulation from the nasal cavity.[27]

## 7. Challenges and Future Perspectives

Although nasal in situ gels have great potential, they face several challenges[6]:

**Device Compatibility**: The formulation and device development challenge lies in ensuring a consistent delivery of the gel-forming solution as a fine spray without clogging the actuator.[3]

**Irritancy:** High polymer concentrations or permeation enhancers can cause irritation or damage to the nasal mucosa.[14]

**Dose Volume Limitations:** The maximum allowable dose volume per nostril is limited (25-200 µL), which restricts the total dose that can be delivered, especially for potent drugs.[1]

**Scale-Up**: The manufacturing process for these sensitive polymeric formulations is often complex and difficult to scale up.[35]

**Future Perspectives**

The future research is focused on:

**1. Combination Systems:** Formulations using dual mechanisms (thermo- and ion-sensitive) for more effective gelation.[18]

**2. Novel Polymers:** Development of new biocompatible and biodegradable polymers from natural sources.[23]

**3. Nanocarrier-Loaded Gels:** Loading the in-situ gel with drug-loaded nanoparticles, liposomes, or micelles for targeted delivery and improved penetration.[3]

**4. Nose-to-Brain Delivery:** A new area of research in which in-situ gels are being developed for direct delivery of drugs from the nose to the central nervous system (CNS), thus circumventing the blood-brain barrier.[35]

## 8. CONCLUSION

Nasal spray in situ gelling systems represent a significant advancement in intranasal drug delivery by intelligently responding to the nasal environment; they overcome the primary limitation of conventional formulations, rapid mucociliary clearance. This technology not only enhances the bioavailability of systemically acting drugs, including challenging biopharmaceuticals, but also improves the therapeutic efficacy of locally acting medications. While challenges related to device design and large-scale manufacturing persist, the ongoing research into novel polymers, combination strategies, and advanced evaluation techniques promises a bright future for this platform. With continued development, the nasal spray in-situ gels are poised to become a mainstream dosage form for a wide array of therapeutic applications.

## 9. REFERENCES


1. Illum L. Nasal drug delivery: New developments and strategies. Drug Discovery Today, 2012; 7(23–24): 1184–1189.
2. Pires PC, Santos AO, Pinto JF. Nasal drug delivery: A review on formulation and device aspects. Pharmaceutics, 2022; 14(3): 573.
3. Kumar M, Kaushik D, Kaur A. Nasal in situ gels for local and systemic drug delivery. Crit Rev Ther Drug Carrier Syst, 2021; 38(4): 45–78.
4. Mythri G, Kavitha K, Kumar MR. Novel mucoadhesive polymers: A review. J Appl Pharm Sci., 2020; 10(8): 135–144.
5. Jadhav KR, Shaikh IM, Kadam VJ. Nasal in situ gel: A novel approach for nasal drug delivery. Res J Pharm Technol, 2022; 15(3): 1385–1392.
6. Singh RM, Verma A. A review on in-situ gel forming system for nasal drug delivery. Pharm Nanotechnology, 2022; 10(2): 98–110.
7. Carvalho FC, Campos ML, Gremião MPD. Rheological and mechanical properties of in situ gelling systems for nasal administration. Mater Sci Eng C., 2021; 120: 1117-39.
8. Patil S, Sawant K. Chitosan based mucoadhesive nasal in situ gel for enhanced brain delivery of risperidone. Int J Biol Macromol, 2022; 209: 1210–1222.
9. Sharma P, Sharma S, Jain D. Nasal in situ gel: A smart strategy for systemic delivery of antiemetic drugs. Drug Deliv Lett., 2023; 13(1): 22–33.
10. Bhalerao SS, Lala RR, Patil SV. Formulation and evaluation of nasal in situ gel of zolmitriptan using combination of polymers. Indian J Pharm Sci., 2023; 85(2): 410–420.
11. Patel KK, Patel MR, Patel KR. Design and development of nasal in situ gel of carvedilol for brain targeting. Eur J Pharm Sci., 2021; 158: 105653.
12. Nazar H, Fatouh AM, Elshafeey AH. Sustained release nasal in situ gel of ondansetron: Formulation, optimization, and pharmacokinetic study. J Drug Deliv Sci Technol, 2023; 80: 1041-89.
13. Gaur PK, Mishra S, Purohit S. Formulation and evaluation of in situ gel of propranolol hydrochloride for nasal delivery. Future J Pharm Sci., 2022; 8(1): 15.
14. Dumortier G, Grossiord JL, Agnely F. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. Pharm Res., 2006; 23(12): 2709–2728.
15. Ahmed S, Khan S, Ali A. Optimization of thermoreversible poloxamer 407 in situ gel for nasal delivery of sumatriptan. AAPS PharmSciTech., 2022; 23(3): 78.
16. Rathore KS, Nema RK, Sisodia SS. Formulation and evaluation of thermoreversible in situ nasal gel of metoclopramide HCl. Asian J Pharm Clin Res., 2021; 14(6): 102–110.
17. Gupta H, Jain S, Tiwari G. pH triggered in situ gel forming system for intranasal delivery of lorazepam. Drug Dev Ind Pharm., 2021; 47(5): 765–775.
18. Kulkarni AD, Vanjari YH, Pande VV. Ion-sensitive in situ gels for nasal administration: Formulation considerations. Pharmaceutics, 2022; 14(8): 1625.

19. Nalini T, Basha SK, Siraj S. Natural polymer-based in situ gels for nasal drug delivery: A recent update. Int J Biol Macromol, 2023; 225: 1234–1248.
20. Agrawal AK, Gupta PN, Vyas SP. Chitosan-based in situ gel for nose-to-brain delivery of insulin. J Drug Target, 2020; 28(4): 385–397.
21. Chaturvedi M, Kumar M, Pathak K. A review on mucoadhesive polymer used in nasal in situ gel for systemic drug delivery. Polym Bull, 2023; 80(1): 1–28.
22. Davis SS, Illum L. Absorption enhancers for nasal drug delivery. Adv Drug Deliv Rev., 2021; 172: 174–191.
23. Zaki NM, Ibrahim MA. Quality by design (QbD) approach for formulation of nasal in situ gel of an antiemetic drug. AAPS Open, 2023; 9(1): 5.
24. European Pharmacopoeia Commission. European Pharmacopoeia. 11th ed. Strasbourg: EDQM, 2023.
25. Mahajan HS, Gattani SG. In situ gelling system for nasal administration of fluticasone propionate in treatment of allergic rhinitis. J Microencapsul, 2022; 39(1): 45–55.
26. Khan AB, Maurya N, Maniruzzaman M. Development of ion-activated in situ gel for nasal delivery of azelastine hydrochloride. Gels, 2023; 9(2): 115.
27. Singh R, Sharma D, Pandey S. Insulin-loaded mucoadhesive in situ gel for nasal delivery: Development and in-vivo evaluation. J Pharm Innov, 2023; 18(2): 450–462.
28. Hosny KM, Alhakamy NA. Development of a novel combination in situ gel for nasal delivery of donepezil. Saudi Pharm J., 2022; 30(5): 588–599.
29. Garg A, Garg S. Stability indicating studies on nasal in situ gel formulations. J Pharm Biomed Anal, 2021; 195: 1138-42.
30. Elmowafy E, Soliman ME. Ion-activated in situ gel for nasal delivery of a model protein: Formulation and ex-vivo evaluation. J Drug Deliv Sci Technol, 2023; 79: 1040-52.
31. Choi HG, Jung JH. Gamma scintigraphic evaluation of in situ gelling nasal spray in rabbits. Nucl Med Biol., 2021; 96–97: 28–35.
32. Bhatt R, Singh M. Ciliotoxicity evaluation of novel permeation enhancers for nasal in situ gels. Toxicol Mech Methods, 2023; 33(1): 34–42.
33. Ahsan F, Arnold JJ. Influence of formulation variables on spray characteristics of nasal in situ gels. Drug Dev Ind Pharm., 2022; 48(4): 155–165.
34. D'Souza R, Mutalik S. Nanostructured lipid carriers embedded in thermosensitive in situ gel for nose-to-brain delivery of risperidone. Int J Pharm., 2022; 624: 1219-98.
35. Agrawal M, Saraf S, Saraf S, Alexander A. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer's drugs. J Control Release, 2020; 327: 291–319.