The Bioscan
AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES
20(4): 1962-1981, 2025 www.thebioscan.com

NASAL IN-SITU GEL DRUG DELIVERY SYSTEMS FOR OSTEOPOROSIS: ADVANCES IN THERMORESPONSIVE AND MUCOADHESIVE FORMULATIONS

Priyavarshini Sivakumar, Kavitha Rajendran*, Damodharan Narayanasamy

Department of Pharmaceutics, SRM College of Pharmacy, Faculty of Medicine and Health Sciences, SRM Institute of Science and Technology, Kattankulathur, India

Corresponding author: Kavitha Rajendran, ORCID ID: 0000-0002-3994-3386;

Email ID: kavithar@srmist.edu.in

DOI: 10.63001/tbs.2025.v20.i04.pp1962-1981

KEYWORDS
Nasal In-situ gel, Osteoporosis, Raloxifene, Bisphosphonates, Mucoadhesive polymers, Thermoresponsive delivery, Bioavailability enhancement, Drug delivery system, GRAS excipients, 505(b)(2) pathway.

Received on:

25-10-2025

Accepted on:

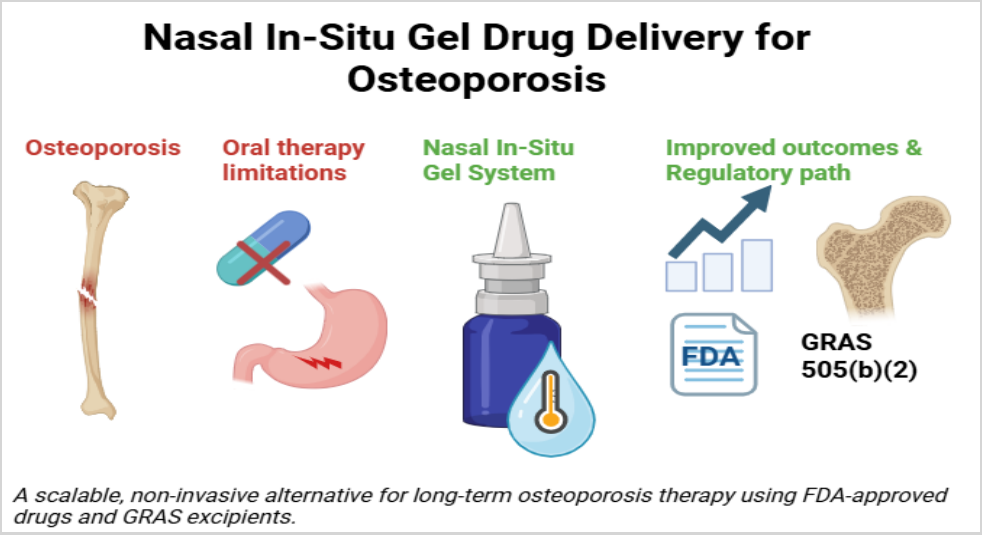
07-11-2025

Published on:

31-12-2025

ABSTRACT

Osteoporosis is a chronic metabolic bone disorder requiring sustained pharmacotherapy. Conventional oral drugs such as raloxifene and bisphosphonates are limited by poor bioavailability, gastrointestinal intolerance, and poor patient compliance. Nasal in-situ gel drug delivery systems represent a thrilling alternative by combining the advantages of the nasal route with the application of temperature-sensitive and mucoadhesive polymers to enhance drug absorption and residence time. This review emphasizes recent progress in nasal in-situ gel formulation for osteoporosis treatment, with attention to formulation approaches, pharmacokinetics, efficacy, safety, and regulatory aspects. The studies have shown increased systemic bioavailability (up to 13.4-fold for raloxifene), increased bone mineral density, and non-irritating, stable formulations appropriate for long-term administration. Further, employing FDA-approved drugs and GRAS-listed excipients allows development through the 505(b)(2) regulatory route. Although formulation achievement is met, limitations of nasal volume, mucosal tolerability, and clinical translatability still exist. Nasal in-situ gels are well-positioned to be non-invasive, scalable candidates for efficacious osteoporosis treatment.



INTRODUCTION:

Osteoporosis is a chronic metabolic bone disease characterized by a gradual loss of bone mass with microarchitectural deterioration, which translates into leanness of bone and increased susceptibility to fragility fractures(1). The burden of osteoporosis weighs heavily in Asia, where demographic changes toward the formation of aging populations presage a rapid rise in osteoporotic fractures and concomitant health care costs(2)

Treatment of osteoporosis largely involves oral antiresorptive medications such as raloxifene, which is a selective estrogen receptor modulator (SERM), and risedronate, which is a bisphosphonate. But these drugs have poor oral bioavailability because of extensive hepatic first-pass metabolism, and most patients cannot bear their long-term use due to irritation of the gastrointestinal tract, thereby affecting patient compliance and therapeutic outcome(3)

Due to such limitations, intranasal drug delivery offers an interesting, non-invasive, and efficient systemic mode of drug delivery. The very vascularized nasal mucosa provides a direct pathway into systemic circulation, thereby bypassing gastrointestinal absorption and hepatic first-pass metabolism, and the antiosteoporotic drug's pharmacokinetic profile can be enhanced (4)

Such further developments can be seen through in-situ nasal gel outcome, which are liquids at room temperature and gel upon contact with the nasal mucosa, as physiological conditions of temperature or pH trigger such transformation. In this manner, newer gels can enhance mucosal adhesion and increase the residence time to promote sustained release of drugs and better absorption of drugs(5)

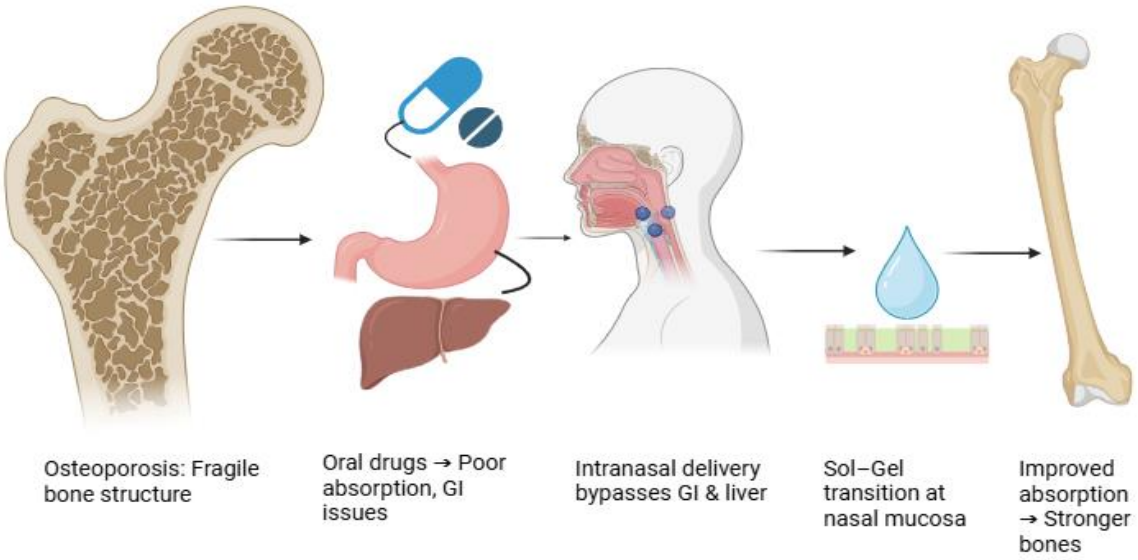


Figure 01: Conceptual illustration showing the basis of nasal in-situ drug delivery for osteoporosis. Oral therapy suffers from issues such as poor bioavailability and gastrointestinal irritation. The nasal in-situ gel is a non-invasive alternate route with good mucosal retention and systemic absorption.

"FROM NOSE TO BRAIN: REIMAGINING CHRONIC THERAPY VIA INTRANASAL DELIVERY"

Nasal drug delivery is a non-invasive and patient-friendly mode of drug administration, especially suited for chronic disorders such as osteoporosis. It facilitates self-administration without injections or clinical supervision, thus improving patient compliance (6) Further, the nasal mucosa is rich in blood vessels and hence absorbs drugs fast, providing a quicker onset of therapeutic action when desired (7)

Nasal delivery serves chronic therapy and systemic drug administration on a much larger scale. In contrast to topical or localized nasal therapies, in-situ gels and nanosystems intended for nasal application have indicated encouraging results for systemic bioavailability (8) Hence, in the case of long-term therapies, such as those found in bone disorders, cardiovascular diseases, and hormone regulation, the nasal route can be a potential replacement for oral or injectable systems.

In addition, the nasal route circumvents the deleterious gastrointestinal conditions and bypasses first-pass metabolism, which is suitable for the delivery of macromolecules that are labile or have low bioavailability. Enzymes in the GI and liver metabolism of certain drugs, such as peptides, hormones, and drugs with low solubility, may be degraded by these systems and could

be more effectively delivered as nasal sprays(9,10) This improves drug stability and bioavailability.

In addition, transport of drugs through the nasal route is ideal in cases where frequent administration is required, such as in the treatment of osteoporosis. The option of intranasal administration is a more comfortable way of medication with less discomfort and fewer complications of repeated injections or long-term oral therapy, particularly in the elderly (11,12) The addition of mucoadhesive and thermosensitive in-situ gel properties of nasal systems led to the prolonged residence time of the dosage form and drug release, supporting the administration of these systems for chronic therapeutic regimens.

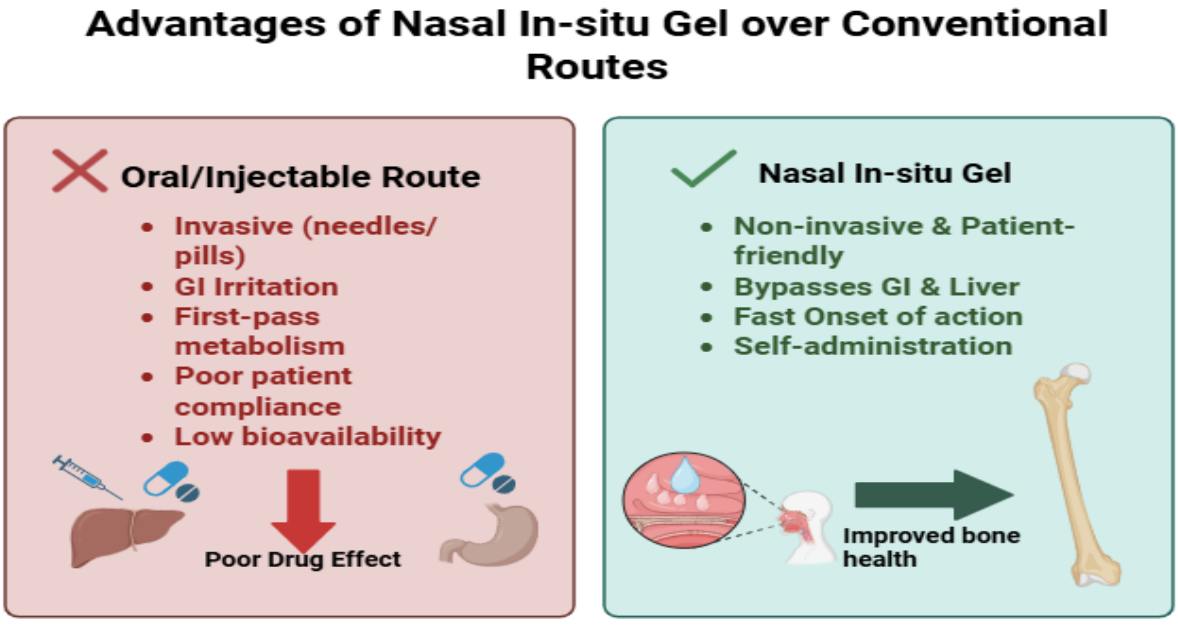


Figure 02: Comparison of conventional (oral/injectable) drug delivery routes versus nasal in-situ gel systems. The nasal route provides improved systemic delivery, avoids GI metabolism, and enhances patient compliance, making it particularly suitable for chronic therapies like osteoporosis.

MECHANISTIC INSIGHTS INTO THERMORESPONSIVE AND MUCOADHESIVE IN-SITU GELS

An in-situ gelling system is an advanced platform for drug delivery wherein the liquid formulation is induced to gel upon contact with physiological triggers such as temperature, pH, and ionic strength (13,14) Thermoresponsive in-situ systems have become favourable in nasal drug delivery owing to the ease of administration and increased patient compliance. Being a predominantly employed thermosensitive polymer, Poloxamer 407 retains its state of sol to

temperature at room temperature, but gels at nasal cavity temperature (-32-34°C) through the aggregation of micelles, thereby providing localized retention and lowering mucociliary clearance(5,15)

Mucoadhesive polymers like Carbopol 934, chitosan, and HPMC are added to the formulation to increase adhesion to mucus and prolong the retention period(16,17) These place the gel at the absorption site by forming a hydrogen bond and interacting electrostatically with the nasal mucosa (18) The mucoadhesive sol-to-gel transition makes the system useful for the sustained release of drugs and also shields the drug from being degraded by enzymes, which is especially useful for drugs that need to be administered at frequent or systemic levels, for example, anti-osteoporotic drugs(19)

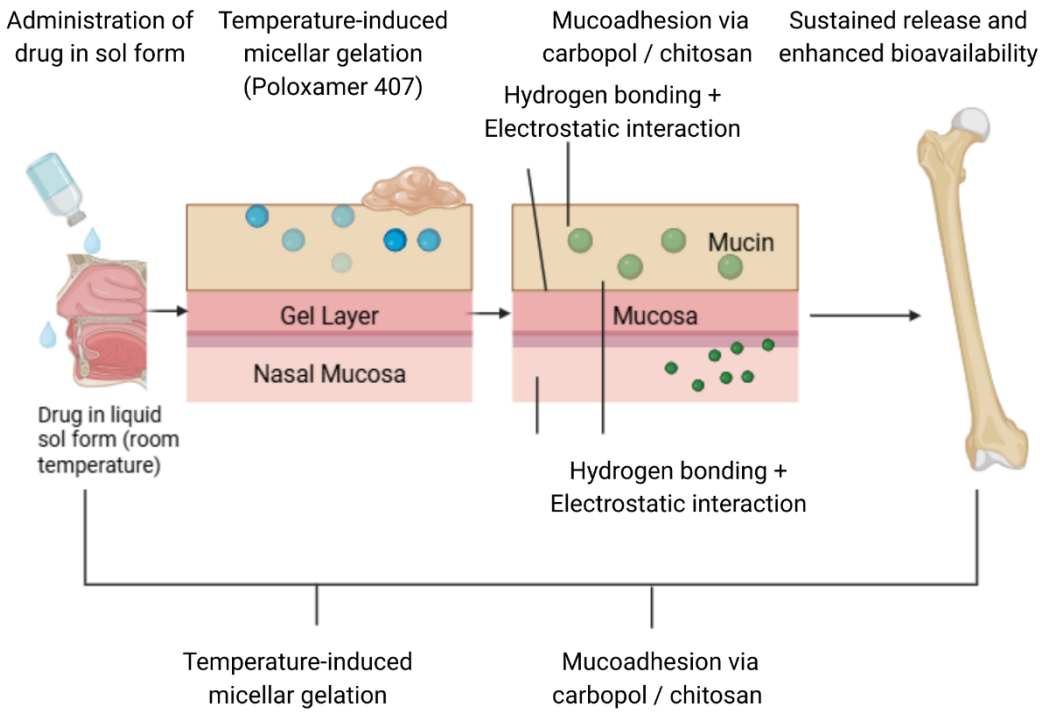


Figure 03: Sol-to-gel transition triggered by nasal temperature, with mucoadhesive polymers anchoring the gel to mucosa, enhances retention, reduces clearance, and supports sustained drug release.

Table 01: Formulation Components used in In-situ Gelling Systems for Osteoporosis and Nose-to-brain drug delivery

Ingredient type	Example	Role in Formulation	Reference
Drug	Raloxifene HCl, Alendronate, Temozolomide	Therapeutic agents for osteoporosis or brain cancer	(3,7,20)
Gelling polymer	Poloxamer 407 Poloxamer 188	Thermoresponsive sol-gel transition	(3,20)
Mucoadhesive polymer	Carbopol 934, HPMC, Chitosan	Enhances adhesion to the nasal mucosa	(3)
Surfactant	Labrasol	Solubilizes the drug, enhances permeability	(20)
Co-surfactant	Transcutol P	Improves interfacial flexibility, enhances solubility	(20)
Oil phase	Triacetin	Solubilizing medium for lipophilic drugs	(7,20)
Biodegradable polymer	PLGA	Sustained-release matrix (for injectable in-situ gel)	(7)
Vehicle/Base	PBS, Water, Purified water	Maintains isotonicity, facilitates gel formation	(3,20)
Preservative	Benzalkonium chloride	Prevents microbial growth in nasal formulations	(3)

RALOXIFENE NASAL IN-SITU GEL: A PROMISING PLATFORM FOR ENHANCED SYSTEMIC DELIVERY

Raloxifene hydrochloride (RLX), a selective estrogen receptor modulator or SERM, is famous for its usage in treating postmenopausal osteoporosis. Nevertheless, oral delivery suffers immensely due to the drug's extremely poor aqueous solubility and low bioavailability (-2%),

owing basically to extensive first-pass hepatic metabolism and very little permeability through the intestine (21,22)These inherent drawbacks prompted a probe into alternate, non-invasive routes of administration, such as intranasal, coupled with new technological formulations like in-situ gelling systems.

This differentiated study observed the development of a micelle-based delivery system made into in-situ gel, termed misemgel, for nasal delivery of raloxifene hydrochloride. Contrary to a typical nanoemulsion, the new process involves micelles with an in-situ thermoresponsive gel made mainly of poloxamer 407. This block copolymer exists as a sol at room temperature but, at nasal temperatures (-32-34°C), gels rapidly to promote retention in the nasal cavity. The dual-action system would have improved the solubility of raloxifene by micellar entrapment and, by virtue of gelling, prolonged nasal residence time.(23)

The micellar in-situ gel significantly improved the nasal delivery of raloxifene hydrochloride by enhancing solubility and combining the properties of thermoresponsive gel formation and mucoadhesion. The study found that ex vivo permeability tests demonstrated better mucosal penetration than both plain gel and oral tablet formulations, while fluorescence microscopy provided evidence of enhanced mucosal retention through nasal epithelial adherence. The pharmacokinetic analysis of the formulation showed 4.79 times greater bioavailability than plain gel and 13.4 times better bioavailability than oral tablets while sustaining plasma concentrations between 12 and 24 hours. These results fall in line with reports encompassing the use of poloxamer and Carbopol-based systems(24,25) and provide further evidence that micellar in-situ nasal gels can serve as an inhibited nose-to-brain pathway for the non-invasive and effective chronic delivery of poorly bioavailable drugs such as raloxifene.

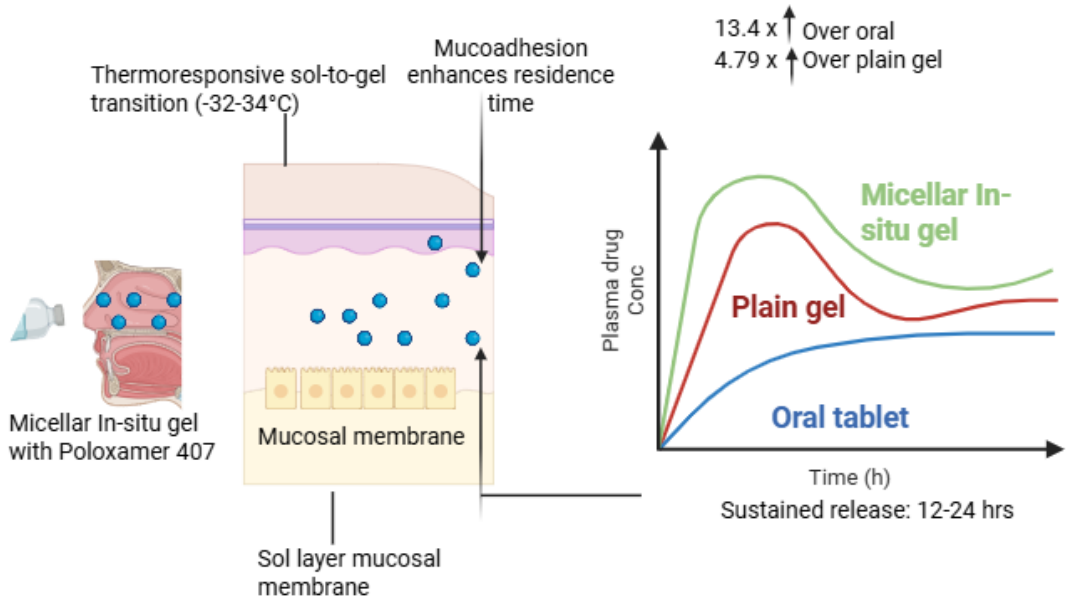


Figure 04: Micellar in-situ gel of raloxifene undergoes temperature-triggered gelation in the nasal cavity, improving retention and permeability. In-vivo studies showed significantly enhanced bioavailability and prolonged systemic levels compared to oral and plain gel formulations.

RISEDRONATE MUCOADHESIVE AND THERMORESPONSIVE GELS FOR INTRANASAL OSTEOPOROSIS THERAPY

Delivery through non-invasive methods can be a tempting strategy to circumvent risedronate's low oral bioavailability and gastrointestinal side effects. These researchers fabricated the novel thermoresponsive in-situ gel with star-shaped poly(oligoethylene glycol) methacrylate (PEGMA) copolymers for nasal use. The gel exhibited a gelation temperature of 34°C, which allowed rapid sol-to-gel transition at this temperature of the nasal cavity. Having mucoadhesive properties, the formulation ensured longer residence time at the nasal mucosa, and ex vivo permeation seemed better into the mucosa than the aqueous solution. The formulation greatly improved bone mineral density and trabecular architecture in glucocorticoid-induced osteoporosis rats and exhibited a better anti-osteoporotic effect than intravenous risedronate. (26)

A mucoadhesive liposomal delivery system for risedronate was developed to improve its nasal absorption. The liposomes were surface-modified to provide greater interaction with the nasal mucosa, thus achieving better in vitro mucoadhesion, controlled drug release, and significantly

higher in vivo bioavailability. Their system reports powerful binding to the mucosa with long-term systemic levels, thus providing assurance to the notion of mucoadhesive systems being vital in intranasal delivery of bisphosphonates. Overall, these studies underscore the capability of liposomal encapsulation and thermoresponsive gels, particularly when combined with mucoadhesion, to supply advanced solutions to effective, non-invasive osteoporosis treatment with risedronate (27)

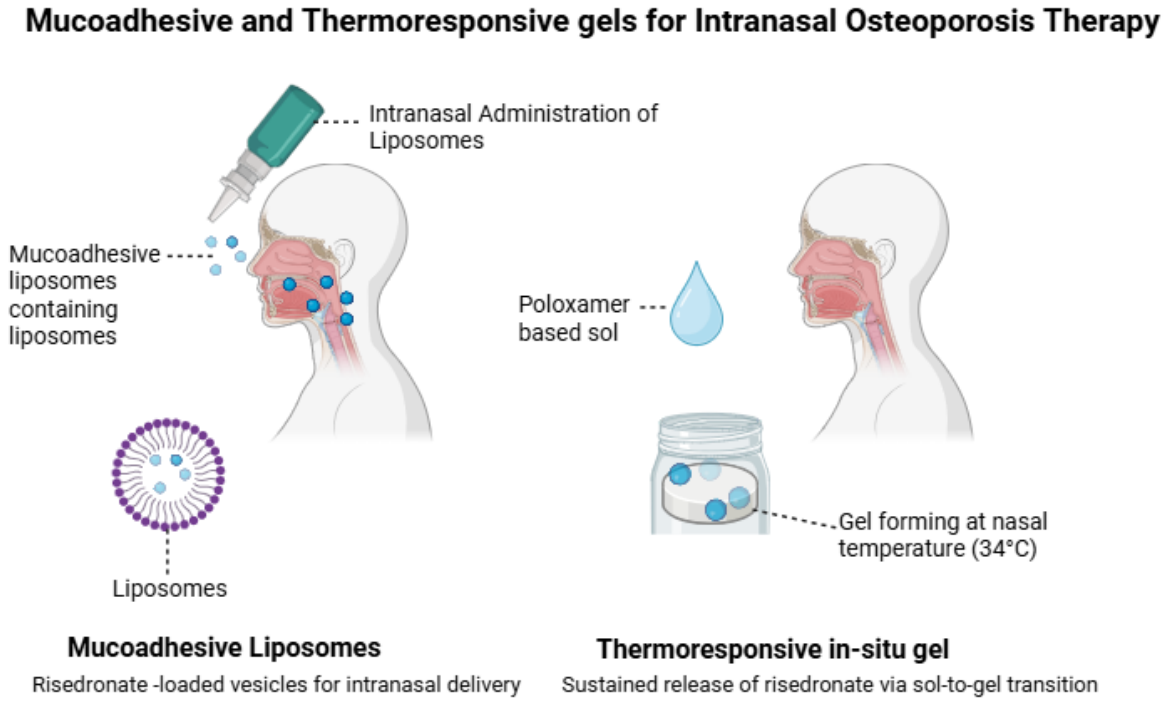


Figure 05: This figure compares two advanced systems for intranasal delivery of risedronate: (1) mucoadhesive liposomes that enhance nasal transition and bioavailability, and (2) thermoresponsive in-situ gels that transition to a gel at ~34°C, prolonging residence time and enabling sustained drug release.

NASAL IN-SITU GEL: EVALUATION PARAMETERS

A complete set of evaluations is critical for these formulations since they must ensure formulation stability, compatibility with nasal physiology, and efficacy of these formulations. All formulations tested possessed good clarity, with a pH range between 5.0 and 6.5 to prevent irritation of the mucosa(3,7). Gelation time was at 32–34°C, coinciding with the nasal temperature responsible for rapid sol-gel transformation(26). The viscosity study confirmed lower fluidity for administration with an adequate gel strength. A texture analyser measured the mucoadhesive strength, and it was found that there was a strong bind to the mucosa, thanks

to Carbopol 934 and chitosan, which allow for prolonging the residence time within the nose(3). Similar investigations on Salmon Calcitonin gels confirmed the reproducibility of these evaluations(28)

In-vitro release experiments revealed a sustained release of Raloxifene and Risedronate for 24 hours, implying infrequent doses with higher patient compliance (7)Ex vivo permeation studies employing goat nasal mucosa showed a higher permeation capability from the in-situ gels than from the plain drug gels, accounting for greater mucosal absorption(3). Histopathological investigations in all relevant studies showed that the formulations proved safe, lacking in evidence of epithelial or ciliary toxicities, further proving promising for concurrent long-term nasal administration(3,28)

Table 02: Summary of Evaluation Parameters for Nasal In-situ Gels

Parameter	Observation/ Result	Purpose/ Significance	Reference
Clarity	Clear, no phase separation	Ensures formulation stability and patient acceptability	(3)
pH	5.0-6.5	Mucosal compatibility avoids irritation	(7)
Gelation Temperature	32 – 34°C	Enables rapid sol-to-gel transition upon administration	(26)
Viscosity & Gel Strength	Low pre-gel, adequate post-gel	Ease of administration, retention in the nasal cavity	(3)
Mucoadhesive strength	Strong with Carbopol/ chitosan	Prolongs residence time for better absorption	(3)
Texture Profile	Good firmness consistency	Ensures user comfort and mechanical integrity	(3)
In Vitro Drug Release	Sustained up to 24 hours	Reduces dosing frequency, enhances patient compliance	(7)
Ex vivo Permeation	Higher than plain gels	Indicates enhanced mucosal absorption	(3,28)
Histopathology/ SEM	No epithelial or ciliary damage	Confirms biocompatibility for long-term nasal use	(3,28)

PHARMACOKINETIC AND EFFICACY OF IN-SITU GEL DRUG DELIVERY SYSTEMS IN OSTEOPOROSIS

Treatment of osteoporosis by targeting bioavailability and reducing the frequency of dosing through in-situ gels has opened vistas in improving the pharmacokinetics and hence the therapeutic effectiveness of anti-osteoporotic drugs. Raloxifene, a SERM, has poor bioavailability of about 2% because of hepatic first-pass metabolism (29) Upon nasal administration through an in situ mistemgel, the drug exhibited a 13.42-fold increase in bioavailability, with a Tmax of 0.5 hour and a significantly higher Cmax of 580.5 ng/ml when compared to oral administration (23) Nasal administration of the drug via in situ thermomist gel showed a 13.42-fold increase in bioavailability, with a Tmax of 0.5 hour and a far higher Cmax of 580.5 ng/ml than oral administration (23) The results raised the following two absorption path considerations through nanoemulsion: transcellular absorption, through edible micelles, and paracellular absorption. On the other hand, risedronate administered through thermosensitive nasal in situ gels also increased bone mineral density (BMD) by 162%, decreased the number of osteoclasts, and modulated markers of bone turnover (↑BALP, ↓TRACP) in ovariectomized rats (3)

On the contrary, having 0.6% bioavailability when orally given, alendronate suffers gastrointestinal side effects(30), and so it was converted into a parenteral formulation comprising IM in situ gels for sustained release using the PLGA and PCL polymers. According to (7) the considered formula increased bioavailability by 13 times and extended the MRT to 102 ± 8 days, as against just 4 days of a simple aqueous injection. This polymer system ensures controlled release for 3 months and thus could serve as a good alternative to frequent oral dosing. While it agrees that the considered route was a bit different from nasal delivery, it does show the nimbleness of the in situ gel systems to address osteoporosis management for chronic use.

Table 03: Pharmacokinetics and efficacy of Situ Gels in Osteoporosis

Drug	Route	Formulation type	Pharmacokinetic Result	Efficacy Outcome	Reference

Raloxifene	Nasal	In-situ misemgel (micelle + gel)	↑13.4× bioavailability Tmax= 0.5 h, ↑Cmax, ↑AUC	Improved systemic exposure with sustained release	(23,29)
Risedronate	Nasal	Thermoresponsive in-situ gel	Improved mucosal absorption	↑162% BMD, ↓osteoclasts, improved biomarkers	(3)
Alendronate	IM (intramuscular)	Biodegradable depot in-situ gel	↑13× bioavailability MRT: 102 ± 8 days	Sustained release over 3 months, reduced dosing frequency	(7,30)

REGULATORY RELEVANCE

The nasal in situ gel systems for raloxifene, risedronate, and alendronate indeed represent reformulations of already FDA-approved oral drugs. This allows them to pursue development via the 505(b)(2) regulatory pathway, a unique hybrid application that uses existing data on safety and efficacy to drastically shorten development timelines (31) This route is especially appropriate for the reformulation of drugs such as raloxifene, for which very long-term clinical evidence demonstrates a reduction in fracture risk in postmenopausal osteoporosis (32)

The excipients most widely used in nasal in situ gels – Poloxamer 407 (a temperature-sensitive polymer) and Carbopol 934 (an adhesive agent) – are recognized as GRAS (Generally Recognized as Safe) by the U.S.FDA. Their long-standing safety records and extensive use in

commercially available nasal and injectable products lend support to their acceptance by the regulatory authorities in new dosage forms(3)

Additionally, these in situ gel systems can be conveniently scaled up to commercial levels via simple mixing and cold processing procedures. They have already been proven to possess physical stability, mucosal compatibility, and therapeutic efficacy in preclinical models and hence show great promise for clinical translational and commercialization as nasal sprays or gels (3)

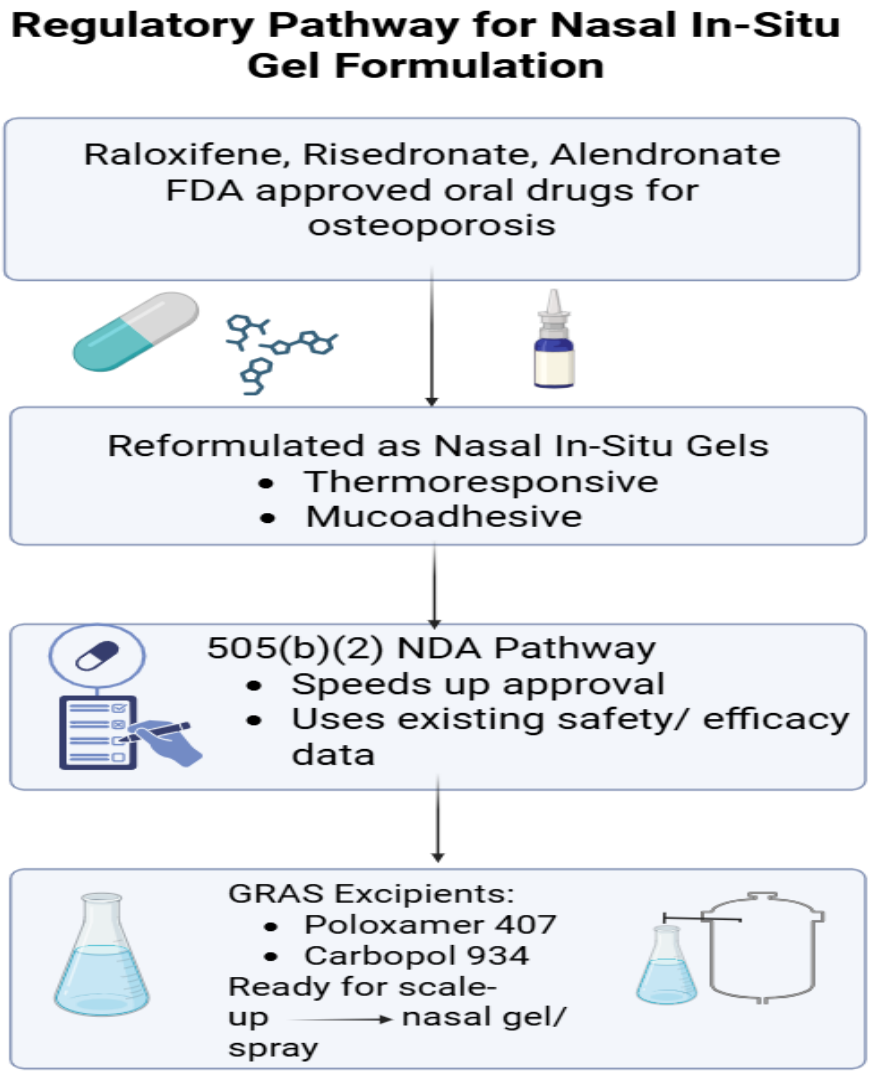


Figure 06: Regulatory pathway for nasal in situ gel reformulation of FDA-approved osteoporosis drugs using GRAS excipients and the 505(b)(2) NDA route, enabling faster approval and commercialization.

CHALLENGES AND LIMITATIONS

While they are promising in their benefits, nasal in-situ gel formulations are afflicted with several major challenges and limitations that must be addressed before their clinical translation. One significant limitation is the low volume capacity of the human nasal cavity, typically capped at 100–200 µL, which limits the dose of drug that can be delivered to its highest (23).Moreover, rapid mucociliary clearance and enzymatic degradation in the nasal environment could lead to decreased residence time and bioavailability, and hence, effective mucoadhesion characteristics and sustained release mechanisms are needed(3).Prolonged use may also result in potential mucosal irritation or local toxicity when poorly optimized formulations are chronically employed without rest periods.

Yet another key limitation is the unavailability of human clinical data. Most safety and efficacy evaluations have been done in preclinical animal models, and there are translational gaps that exist for mucosal absorption heterogeneity, patient compliance, and large-scale pharmacokinetics. Moreover, regulatory guidelines for nasal in-situ gels continue to evolve and scale-up for commercial manufacturing poses demanding stability, sterility, and packaging solutions. These issues accentuate the requirement for ongoing optimization of formulation and properly designed clinical trials to confirm long-term safety and therapeutic efficacy in humans.

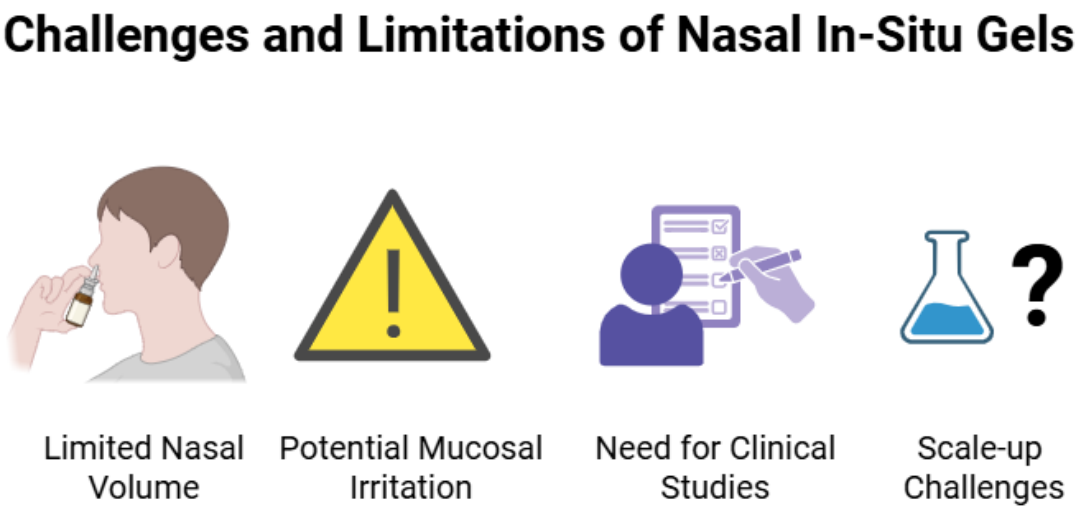


Figure 07: Major limitations associated with nasal in situ gel delivery systems include the restricted dosing volume of the nasal cavity (100-200 µL), potential for mucosal irritation with long-term use, the current absence of human clinical data, and challenges in formulation scale-up for commercial manufacturing.

CONCLUSION

Nasal in-situ gel systems represent an excellent advance in chronic disease treatment, such as osteoporosis, for drugs like raloxifene, risedronate, and alendronate with poor oral bioavailability and gastrointestinal side effects. The drug delivery systems utilizing thermoresponsive and mucoadhesive properties of polymers such as Poloxamer 407 and Carbopol 934 ensure improved nasal residence, controlled drug release, and improved systemic absorption. Pharmacokinetic advantages observed—e.g., raloxifene with an increase in bioavailability of 13.4 and risedronate with large benefits to bone mineral density—highlight the potential value of nasal gels as a pain-free alternative to conventional oral and injectable agents.

Despite these encouraging outcomes, there are several issues that hinder near-term clinical application. They include the limited volume capacity of the nasal cavity (100–200 µL), potential mucosal irritation through chronic dosing, and a lack of strong human clinical data. Also, large-scale production and regulatory standardization need to be optimized.

In the future, combining modern polymers, patient-specific delivery devices, and practical clinical trials will be important to achieve the complete therapeutic potential of nasal in-situ gel systems. The 505(b)(2) pathway provides an expedited approval process for these reformulated products so that commercialization will become a reality. Through further research and interdisciplinarity, nasal in-situ gels will potentially become a convenient, patient-compliant treatment for chronic osteoporosis.

Acknowledgment

The authors are thankful to the management of SRM College of Pharmacy, Faculty of Medicine and Health Sciences, SRMIST, Kattankulathur, for their never-ending help and support.

Author contribution

Priyavarshini Sivakumar– Conceptualization, Methodology, Writing - original draft, Writing - review and editing. **Kavitha Rajendran** - Project administration, Supervision, Writing - review and editing. Damodharan Narayanasamy- Visualization, Writing - review, and editing.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

Funding

This work received no funding.

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