



A Comprehensive Review on In-Situ Gel Drug Delivery System

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Abstract



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Over the past ten years, in situ gelling drug delivery methods have attracted a lot of attention. Prior to injection, they are in a sol-state, and they can gel when exposed to a variety of endogenous stimuli, including temperature rise, pH changes, and the presence of ions. Such to accomplish the injection of a local or systemic medication, systems may be delivered by a variety of can also be employed effectively as carriers for nano- and microparticles that carry drugs. Natural or artificial or in conjunction with semi-artificial polymer exhibiting in situ gelling behaviour. For the development of such systems, coupling with mucoadhesive polymers is highly sought in order to prolong the duration spent at the site of action or absorption. Nasal drug administration is a superior option than oral and parental routes because of the high permeability of the nasal epithelium, rapid drug absorption, avoidance of hepatic first pass metabolism, improved bioavailability of the medication, and fewer adverse effects. adverse local and systemic effects, minimal dosage is required, Patient compliance has increased, direct distribution to the CNS and systemic circulation is available, and self-medication. The development of gastric ulcers can be prevented. Recent evidence indicates that many medications have greater oral bioavailability than nasal bioavailability. So, the focus of this review is on nasal drugs. Administration, various nasal architecture and physiology characteristics, the method of nasal absorption, and benefits, Evaluations of in situ gels' composition, use, and advantages and disadvantages.

Keywords: Nasal formulation, sustained drug administration, mucoadhesive drug delivery system, and in-situ nasal gelation.

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Introduction:

The olfactory pathway is a crucial method for delivering medications, a growing selection of medications, including those for allergic diseases and regional and systemic effects, are now able to be administered using this method. Nasal drug administration recently began using a novel dose type called in-situ gel ¹.

Respiratory topical solutions are infused as reduced viscosity liquids in the nose as opposed to liquid nasal formulations. The nasal passageway. The polymer changes structure as it comes into touch with the nasal mucosa, creating a gel such that it can both increase the amount of time that the drug is in contact with the locations for absorption in the nasopharynx, but also gradually and constantly delivers medication ^{2,3}.

The creation of in-situ gelation medication delivery methods, particularly via the nasal route, has drawn more and more attention in scientific research during the past ten years. Most of these systems exhibit the distinctness of being in a sol-state prior to injection and to undergo cavity gelation. Consequently, we learn the significance of simple administration, extended occupancy, and long-term medication delivery, a decrease in dosage repetition, and a rise in patient comfort and obedience. One of the factors for these

enormous success formulations, there is the ability for them to be supplied via a variety of achieve a systemic or localised impact of the drug loaded ^{4,5,6}.

Mucociliary clearance is the physiological factor that is principally responsible for the shorter drug residence length, within the nasal cavity, given that the intranasal route has various advantages in terms of accessibility, efficacy, tolerability, and patient compliance⁷. This self-clearing mechanism is what causes the fast medication clearance from the nasal cavity, cutting down on the amount of time required for the medication for treating nasal local disorders, getting into the systemic bloodstream, or CNS ^{8,9,10}.

Anatomy and Physiology of Nasal Cavity^{11,12} -

The nostril on each side of the nasal vestibule, which is the nasal cavity's most anterior section, allows access to the face. The nasopharynx is split in half by the mucous membrane, while the nasal cavity extends posterior to the nasopharynx. The primary senses of breathing and smell are the nose's functionality, but it also before the air reached the lowest airway, it served as filtering and humidified the air that was inhaled ^{13,14}. The mucus layer and hairs in the nasal cavity are useful in filtering out trapped particles in air breathed. The size of the adult nasopharynx is 180 cm², with a total capacity of 16 to 19 mL, is split in half by the septum into two nasal

cavities. Each cavity is approximately 7.5 mL in capacity and 75 cm² in surface area.

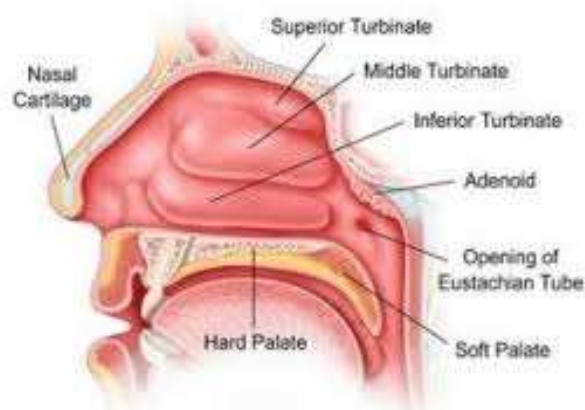


Figure 1: The nasal cavity's anatomy ¹⁵

1. The Respiratory region- The largest and most vascularized part of the body, the respiratory region is primarily in charge of systemic drug absorption. There are four different cell types that make up the respiratory epithelium. Specifically, basal cells, goblet cells, and non-ciliated and ciliated columnar cells. These Active transport activities including the exchange of ions and water are made possible by cells. Between the movement of cilia within cells. They could also be used to stop drying of the mucosa through moisture absorption.

ANATOMY OF NASAL MUCOSA

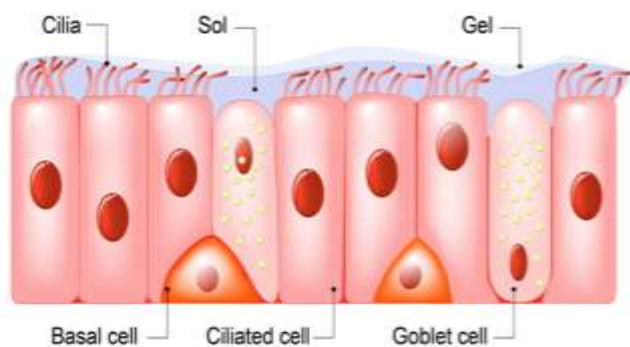


Figure 2: Nasal Epithelium Cell Types ¹⁶

2. The olfactory region- Its width is approximately 10 cm², and it is essential for medication delivery to the brain and CSF. Just below the cribriform plate of the nasal cavities' ceiling lies where the olfactory region, The nostril canals and cranial chamber are separated by the ethmoid bone. The nasal mucosa frequently has a yellow colour, as opposed to the pink tissue that surrounds it. While breathing is the primary function of the nostrils in humans.
3. The Vestibular region- It is the front portion of the nasal cavity. There are 0.6 cm² of surface. A sebum gland-containing stratified squamous keratinocytes epithelial covers the nasal region. It is situated where the nasal passageways begin, and it is accountable for removing airborne pollutants. Drug assimilation is extremely Although it was challenging in this area, it provided strong resistance against the hazardous environment. It is

regarded as the least significant of the three in terms of drug absorption.

Drug Absorption via Nasal Route Mechanism¹⁷:

The mucus layer must be penetrated for the medications that be absorbed from the nasal cavity. It is the initial phase of assimilation. Large, charged medications find it challenging to penetrate through this barrier, but small, unaltered molecules can easily do so. Mucin is the main protein in mucus. Its propensity to bind to the solutes prevents diffusion. Additionally, Environmental factors may cause the mucus layer's structure to changes.

The two mechanisms that include:-

The first mechanism: It is a sluggish, passive water channel of transport, commonly referred to as the paracellular pathway. Intranasal absorption and the weight of water have an inverse log-log relationship. Soluble substances When the molecular weight exceeds 1000 Daltons, it indicates poor bioavailability.

Second Mechanism- It involves transfer via the transcellular process, a lipoidal pathway. It is in charge of transporting medications with a rate dependence on their lipophilicity. Drugs can also traverse cell boundaries using carrier-mediated transport or active transport, membranes through tight joints' openings. As an illustration, chitosan, a natural biopolymer derived To enable medicine delivery, shellfish relax tight connections between epithelial cells.

Advantages of In-situ Nasal Gel Formulation ¹⁸:-

- Rapid absorption and commencement of effect due to increased time the drug spends in the nasal cavity and decreased frequency of drug delivery.
- Prevents drug breakdown in the digestive system due to enzymatic or acidic breakdown.
- Low dosage necessary.
- Reduced systemic and local side effects.
- Increased drug bioavailability.
- Direct transit into the CNS and systemic circulation is possible.
- Reduces the chance of a CNS acting drug overdose.
- Increased adherence of the patient.

Disadvantages of In-situ Nasal Gel Formulation:- ¹⁹

- Unknown drug transportation method.
- Surface area is smaller compared to GIT, and only a little volume can be sprayed.
- Appropriate for powerful drugs.
- Dosage loss as a result of mechanical and technical factors.
- Mucosal harm.
- Nasal mucosal sensitivity.
- Permanent ciliary injury to the nasal mucosa.

Material and Methods:

Table-1: List of Materials used in Nasal gels²⁰

Sr. No.	Materials
1	Drug
2	Polaxmer
3	HPMC K4M
4	PEG 400
5	Methyl Paraben
6	Water

Formulation of Nasal in- situ Gel:

²¹

By using the cold approach, numerous in situ gel formulations with various drug and polymer ratios are created. Poloxamer is initially dissolved separately in a very little amount of water at a 20 percent w/v concentration. Then, HPMC is dissolved in the appropriate amount within the piece. Methyl paraben, PEG 400, and the medication are added afterwards and mixed. Finally, using pure water, increase the volume to 100 ml and maintain it. Keep it overnight in subfreezing temperatures (4–10 °C).

Assessment of In-Situ Gel

^{22, 23, 24}

Drug Excipient Interactions Research - Fourier Transform studies on drug-polymer interactions. Infrared spectroscopy was used to evaluate the drug sample's purity and its interactions with the polymers. We collected the infrared spectra of the medication and the polymers both separately and together. After that, any potential interactions were looked into compared to the typical IR spectra of the pure drug and the interaction between polymer and drug.

Clarity- The generated formulations underwent a visual examination for on a white background, for transparency, coloration in liquid and jelly form, and for the existence of any particulate matter.

pH of Gel- The pH of each formulation was measured using a pH metre that had previously been calibrated using reference buffers of pH 4, pH 7, and pH 9.

Gelling Thermal Research²⁵ - A modified version of the Miller and Donovan method was used to determine it. The test tubes were filled with a 2 ml aliquot of gel and put in an insulating chamber inside a water bath set at 4 °C. The water bath's temperature rose by an amount of 1°C.

Estimation of Drug Content²⁶⁻ 1 ml of the preparation was diluted with 10 ml of distilled water, which had been taken into the volumetric flask. Once more, 10 ml of purified water were utilized to dilute 1 ml of this solution. At 286 nm, the produced solution's absorbance was lastly measured utilising a UV-visible spectrophotometer, against a blank reagent (Shimadzu UV1800). Last but not least, focus the medication contained in the formulation was calculated using the calibration curve.

Gel Strength- A measuring cylinder containing 100 ml, 50g of nasal gel was obtained as a sample, and it gelled at 37°C in a thermostatically controlled waterbath. A 35g weight was added to the gelled solution. The gel strength, which represents the nasal gel's viscosity at physiological temperatures, The time in seconds required for a mass to puncture a 5 cm thick sheet of gel was used to determine temp.

Viscosity measurement²⁷⁻The Brookfield viscometer was used to conduct the rheological studies. A suitable spindle was chosen and inserted perpendicularly into the gel formulation under study after it had been put in the material holder. The spindle was turning continuously at its best motion. The temperatures ranging from 5°C to 40°C were used to determine the formulation's viscosity.

In Vitro Drug Release²⁸⁻ The in situ gel formulation was subjected to an in vitro drug release assay employing dialysis membrane-70 without the molar mass of 1200- 1400 KDa in a two chambered diffusion cell. Upper and lower chambers made constituted a diffusion cell with specifications of 2.4 cm in diameter and 25 ml in volume. cylindrical container with a diffusion membrane at its base and an open top. making artificial pieces of dialysis membrane were placed on a mounting surface after spending an hour in PBS pH 6.4 cell diffusion A two-chamber cell included the dialysis membrane.

Conclusion-

The study of all the variables and components of the in-situ gelling system is the main topic of the current article. The in-situ gel dosage forms have properties that promote patient compliance, high stability and biocompatibility, and prolonged and sustained drug release. Reliable in-situ gel provides certain advantages over injectable treatment and Non-invasiveness and rapid action are advantages of the oral route. liquid and bioresorbable are used. For nasal methods for in situ gelling systems, a soluble, thermosensitive, and pH sensitive polymer make them a superior drug delivery mechanism that is more palatable. Nasal topical gel due to its mucoadhesive strength and viscosity, it prolonged the nasal residence period. Better mucoadhesive strength, pH, gelation duration, gelation temperature, rheological characteristics, and in vitro release can all be used to achieve the best formulation research on permeability.

Conflict of Interest:

The authors have no conflict of interest.

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