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In Situ Gel: A Novel Alternative For Intranasal Drug Delivery

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ABSTRACT

The oral route stands as the primary method for administering drugs into the body through the mouth. However, this favoured technique encounters several limitations, including challenges with drug absorption, low bioavailability, the obstacle of first-pass hepatic metabolism, and the need for precise drug targeting to specific organs. Due to these hurdles, alternative routes such as the parenteral, transmucosal, and transdermal methods gain preference over the oral approach. A notable advancement in drug delivery aiming to enhance patient safety and effectiveness is the development of the *in situ* nasal drug delivery system. Within this system, drugs are initially administered as a less viscous solution, which upon contact with the nasal mucosa, transforms into a gel. This gel-based formulation via the nasal route proves beneficial for drugs plagued by challenges during oral administration, such as gastric discomfort, poor absorption, low bioavailability, and susceptibility to first-pass hepatic metabolism. The formulation of these gels often involves the use of various triggered polymers.

Key words: *In situ* gel, bioavailability, nasal drug delivery, first pass metabolism, nasal mucosa.

1. INTRODUCTION

Intranasal medication delivery has grown since the 1980s. A non-invasive method of administering active medicinal components for local, systemic, and central nervous system activity is through the nasal mucosa. Despite the nasal epithelium's appearance as a strong barrier, leaky epithelial tissue causes the nasal mucosa's intercellular junctional complex to be less tight. The mucosa, lamina propria, and leaky epithelium are highly vascularized, which also offers an ideal absorption surface for the transport of drugs. The benefits of a direct entry into the brain and a favourable pharmacokinetic/pharmacodynamics (PK/PD) profile for CNS acting medicines are achieved by the direct absorption of the molecules through the trigeminal and olfactory pathways from the nasal cavity. Moreover, this mode of administration offers a novel and promising substitute for enteral and systemic drug administration, enabling the brain parenchyma to be reached by highly effective and powerful CNS-targeted medications by avoiding the primary physiological barriers: Blood-cerebrospinal fluid and blood-brain barriers, respectively. [1]

The nasal route is an important mode of drug delivery, with a growing number of products available for administration through the route for systemic and local administration. Recently, *in situ* gel has been used to administer drugs through the nose. In contrast to previous liquid nasal formulations, nasal *in situ* gels are applied as a low viscosity solution into the intranasal cavity, where the polymer transforms into a gel upon coming into contact with the nasal mucosa. *In situ* gel has remarkable stability, repeatable extended and prolonged drug release, and dependable medicine amounts, rendering it a more precise method.

1.1 Nasal Drug Delivery System

Mainly, intranasal administration is a possibly workable substitute for other medication delivery methods. It is appropriate for delivering a variety of medicinal substances both locally and systemically. As a result, the nasal cavity has been the subject of several studies as a potential venue for the delivery of various medicinal drugs. Treatment of local, systemic, and central nervous system locations is efficacious.

1.1.1 Local

The most natural method for treating topical nasal problems is to provide medications intranasally. Among the most common examples are anti-histamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In these cases, the intranasal route is the primary option for drug delivery because it allows a rapid symptom relief with less side-effect.

1.1.2 Systemic

As an alternative to oral and intravascular methods, intranasal administration is a useful method for delivering medications systemically. As a result, a significant rise in the number of medications designed to produce systemic effects has been achieved through nasal formulations. Analgesics like morphine, cardiovascular medications like propranolol and carvedilol, hormones like levonorgestrel, progesterone, and insulin, anti-inflammatory medications like indomethacin and ketorolac, and antiviral medications like acyclovir are a few well-known examples.[2]

1.2 Anatomy and Physiology of the Nasal Cavity

The nasal cavity is divided into two hales by the nasal septum and extends back to the nasopharynx, while the nasal vestibule is the most anterior portion of the nasal cavity, opens up through the nostril to the nose as shown in fig 1. There are three main regions in the nasal cavity, which are the nasal vestibule, the olfactory region and the respiratory region. The surface area in the nose can be increased by the lateral walls of the nasal cavity around 150cm, which contains a folded structure.[3] When compared with its minor volume, its surface area is very high. This folded structure involves three turbinates: the superior, median and the inferior. The nasal airway has narrow passages which are about 1 to 3 mm wide and which help to perform its principal functions. The mucous membrane that lines the nasal cavity divides into two regions: one for non-olfactory functions and the other for olfactory purposes. In the non-olfactory region, the nasal vestibule is covered with skin-like layers of stratified squamous epithelial cells, while the respiratory region features a typical airway lining with numerous microvilli. This setup offers an extensive surface area that is easily accessible for the absorption and transport of drugs. In this way, the position of the mucus layer from the anterior to the rare part of the nasal cavity is thus shifted. The mucous membrane protects the nasal turbinate and the atrium. The goblet cells secrete mucus as mucus granules that swell in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of approximately 95 % water, 2 % mucin, 1 % salts, 1 % of other proteins such as albumin, immunoglobulin, lysozyme and lactoferrin and 1% lipids. The mucous secretion allows immune response suppression of inhaled bacteria and viruses.[4]

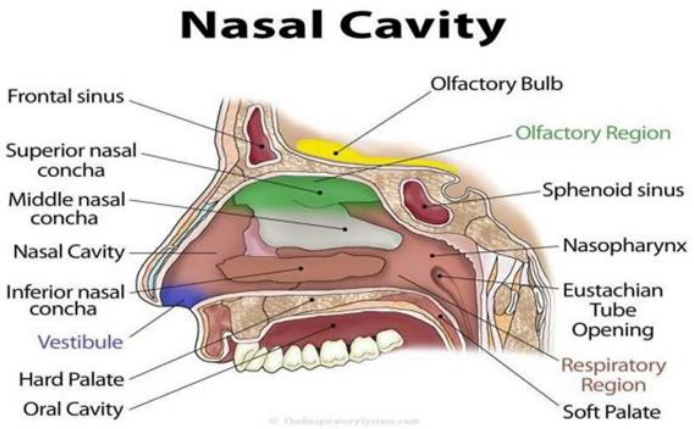

Figure.1 Three regions can be distinguished in each part

1.2.1 Respiratory region

The largest section of the nasal cavity, known as the conchae, is the nasal respiratory region, which plays a crucial role in systemic drug delivery. This area's respiratory epithelium consists of four types of cells: non-ciliated and ciliated columnar cells, basal cells, and goblet cells. Within the respiratory region of the nasal cavity, there are three nasal turbinates: the superior, middle, and inferior, protruding from each side wall. Among these, the nasal respiratory mucosa is crucial for systemic drug delivery.[5]

1.2.2 Olfactory region

Beginning from the upper part of the nasal cavity and continuing briefly along the septum and lateral wall, this area contains the sole neuro-epithelium that directly interacts with the external surroundings. Although housing specific olfactory receptor cells essential for smelling, the olfactory epithelium shares a pseudostratified configuration similar to the respiratory epithelium.[6]

1.2.3 Vestibular region

The nasal vestibule, found just inside the nostrils, represents the most anterior portion of the nasal cavity, covering an area of approximately 0.6 cm. This area is lined with a stratified squamous and keratinized epithelium with sebaceous glands, which filters airborne particles. Although important for its filtering role, the nasal vestibule is generally considered less relevant for drug absorption compared to other nasal regions.

1.2.4 The nature of the nasal mucous membrane

The nasal mucus layer consists of two distinct sections: an outer layer that is thick and sticky, and an inner layer that is a mere 5 μm thin, filled with serous fluid. Comprising 95% of the nasal mucus layer is water, with the remaining 3-5% containing mucin, proteins, lipids, enzymes, antibodies, shed epithelial cells, and bacterial by products.

1.2.5 Epithelial cells

Basically, there are two functions of these cells,

- Structures act as a protective shield, preventing infectious microorganisms and allergens from entering, while the cilia function to generate and eliminate mucus, ridding the nasal cavity of foreign substances.
- They collaborate with mucus glands to fulfil their function.[7]

1.3 Barriers for Nasal Drug Delivery

1.3.1 Low bioavailability

Polar medications often have a poor bioavailability of 10% for low molecular weight medications and no more than 1% for other pharmaceuticals for peptides like insulin and calcitonin.[8] Low membrane permeability is the primary factor preventing the nasal absorption of polar medicines, particularly large molecular weight polar pharmaceuticals like peptides and proteins. Only in small quantities larger peptides and proteins may cross the nasal membrane through an endocytosis transport mechanism.[9]

1.3.2 Mucociliary clearance

The rapid clearance of drugs through mucociliary action in the nasal cavity leads to a decrease in the amount of medication transported through the nasal mucosa. This effect is especially noticeable when the medication is not adequately absorbed through the nasal mucosa. Studies show that both liquid and powder formulations without bioadhesive properties have a clearance half-life of approximately 15-30 minutes.[10] One strategy to overcome rapid mucociliary clearance is to include bioadhesive excipients in the formulations. Enhanced absorption can also be achieved by minimizing clearance, such as by administering the formulation to the anterior, less ciliated area of the nasal cavity.[11]

1.3.3 Enzymatic degradation

Another factor that can contribute to the restricted bioavailability of peptides and proteins across the nasal mucosa is the possibility of enzymatic processes. These processes involve the molecule breaking down either within the nasal cavity lumen or as it traverses the epithelial barrier. Both of these locations are home to endopeptidases like cysteine and serine, which may target internal peptide bonds, and exopeptidases like mono and diamino peptidases, which can cleave peptides at their N and C termini. One way to get around this barrier would be to utilize enzyme inhibitors or to saturate the enzymes.[12]

1.4 Mechanism of Drug Absorption

Drugs intended for systemic or central nervous system (CNS) effects are absorbed through the nasal mucous layer and epithelial membrane and either go straight to the central nervous system or circulatory system. Drug absorption for the systemic impact is thought to occur in the respiratory area, which includes the nasal septum and turbinates. The primary location from which a medication may be absorbed directly into the brain for central nervous system effects is the olfactory area, followed by the respiratory region as shown in fig 2. When a medication is administered intravenously, it can enter the brain directly through the olfactory area, the bloodstream (systemic circulation), or the trigeminal neural pathway, which allows the medication to partially pass from the nasal cavity into the cerebrospinal fluid. As a result, drug molecules acting on the central nervous system (CNS) in conditions such as depression, migraine, schizophrenia, epilepsy, brain tumors, psychosis, pain, and alzheimer's and parkinson’s disease can be targeted to the olfactory region of the nasal cavity, which provides a direct connection between the nose and the brain. The medicine passes through the mucus in the nasal cavity as the first stage in its absorption. Particles that are small and uncharged can readily get past the mucous layer. Large or charged particles, however, can have trouble getting through the mucous layer. The main protein in mucus is mucin which has the ability to attach to solutes and prevent medication from diffusing. There are several ways for a medicine to be absorbed via the mucosa once it has passed through the mucus.[13]

1.5 Advantages

- Potential for rapid drug absorption leading to quick onset of action

- Enhancement of bioavailability for larger drug molecules through the use of absorption enhancers or alternative strategies
- The nasal route is utilized for drugs that exhibit poor stability in gastrointestinal fluids.
- Absence of drug degradation is typically seen in the gastrointestinal tract
- Bypassing hepatic first-pass metabolism
- Nasal drug delivery provides a route for drugs that are not absorbed orally to enter the systemic circulation
- Research conducted to date suggests that the nasal route serves as an alternative to the parenteral route, particularly for protein and peptide drugs
- Drugs with limited oral absorption can reach systemic circulation through nasal administration. [14]

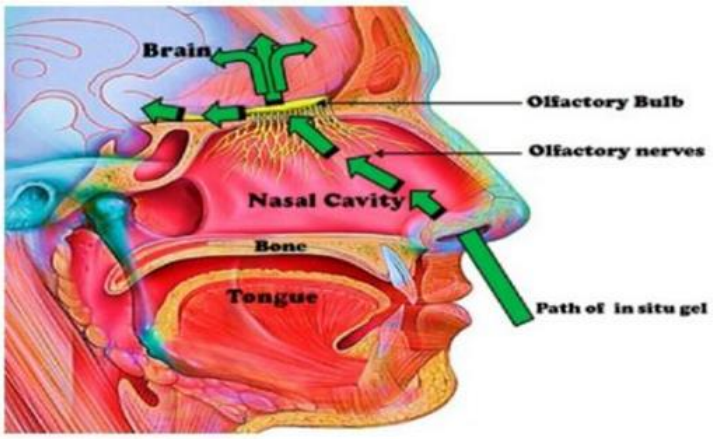

Figure. 2 Position of olfactory bulb with respect to brain and nasal cavity.

1.6 Limitations

- Absorption enhancers utilized in nasal medication delivery systems are histologically harmful
- Patients may have nose discomfort, making it somewhat uncomfortable compared to oral administration methods
- The nasal cavity has a lesser surface area for absorption than the GIT.[15]

1.7 Ideal Characteristic of Drug for Nasal Delivery

The following qualities should be present in a nasal drug candidate:

- Appropriate solubility in water to provide the required dose
- Quick onset of action and low dose, usually less than 25 mg
- No side effects from the medication
- Proper qualities for nasal absorption
- No harmful byproducts in the nose
- No unpleasant smells or scents
- Appropriate stability attributes.[16]

2. INTRANASAL FORMULATIONS AND THEIR LIMITATIONS

Intranasal formulations are available that include nasal drops, solution sprays, suspension sprays, emulsions, powders, ointments, gels, liposomes, microspheres, and nanoparticles. The short residence duration of these non-mucoadhesive formulations is caused by mucociliary clearance when they are delivered in a small amount of 25–200 µl. As a result, the clearance half-life of the liquid and powder formulations is 15–30 minutes. This is mostly because mucus clears out the nose of particles every 12 to 15 minutes at a pace of 5 to 6 mm/min. [17] This causes low nasal bioavailability and restricts the amount of time the medicine may be absorbed from the administered dose form. The development of a controlled release delivery method is still necessary to prevent fast mucociliary clearance and increase the bioavailability of medications. One potential solution is to use mucoadhesive nasal drug delivery systems, which stick to the nasal mucosa and increase the duration of time the drug spends in the nasal cavity. They also help to increase the concentration of the drug at the site of deposition and improve bioavailability by intensifying the contact between the drug and the mucosa.[18]

3. THE ADVANTAGES OF *IN SITU* NASAL GELS OVER OTHER NASAL FORMULATIONS

- Prolong drug release
- Ease of administration
- Better patient compliance
- Reduced systemic side effects
- Minimizes poor taste issues and medication loss from the nasal cavity by reducing post-nasal drip into the back of the throat.[19]

4. IN SITU GEL

When a liquid formulation is administered, it can solidify or become semisolid, which is known as an in situ gel drug delivery method. Systems that undergo a physiological phase change when exposed to circumstances are known as in-situ activated gel-forming systems. In order for gelation to occur, polymer chains must be cross-linked. This can be done either chemically, by creating covalent bonds, or physically, by creating non-covalent bonds.

In situ gel can be administered orally, intraperitoneally, ocularly, rectally, vaginally, or via injection. The condition known as "gel" is a mixture of long polymer molecules that are physically crosslinked and have been inflated by a solvent. Liquid molecules are trapped inside the three-dimensional polymeric network. Prior to injection, this system is a liquid aqueous solution, and under physiological circumstances, it becomes a gel. The in-situ gel is biocompatible, has excellent stability, and consistently releases the drug over an extended period of time, making it more precise.

Recently, a novel dosage form called in-situ gel has been used for nasal medication administration. When compared to other liquid nasal formulations, nasal in-situ gels are applied to the nasal cavity as low viscosity solutions. The polymer then undergoes a conformational change upon contact with the nasal mucosa, resulting in the formation of a gel. This allows the drug to be released gradually and continuously, making it particularly beneficial for chronically used medications. The presence of cations, a change in temperature, or a change in pH can all cause the phase transition.[20]

4.1 Principle of *In Situ* Gelling System

The *in-situ* gelling procedure for solid nasal formulations works on the basis that the nasal formulations absorb the nasal fluid and gel inside the cavity after being administered. The feeling of a foreign body can be prevented by creating nasal gel inside the cavity. Due to its bioadhesive properties, the gel adheres to the nasal mucosa. It works as a matrix to regulate release, allowing for the sustained administration of drugs.[21]

The bottom layer of nasal mucus leaves the nose and circles the cilia, going forward during propulsion and backward during preparation. During the propulsion phase, the cilia extremities scrape the upper layer of mucus, around 0.5 mm. Then, ciliary activity zones sporadically arise at various times. The backward positioning of cilia allows for the efficient removal of any impediments during the propulsion phase. Either breakdown or mucociliary removal to the nasopharynx occurs after gel formation. Consequently, there's no need to take the dose form out after the drug has run out. [22]

4.2 Approaches of *In Situ* Gelling System

Different types of approaches for an *in situ* gelling system are

A) Osmotically induced *in situ* gelling system

B) Chemically induced *in situ* gelling system

- Ionic crosslinking
- Enzymatic crosslinking

C) Stimuli responsive *in situ* gelling system

- pH induced *in situ* gel systems
- Temperature induced *in situ* gel system

D) *In-situ* based on the physical mechanism

4.2.1 Osmotically induced in situ gelling system

In this system, variations in ionic strength cause the fluid to gel. It is believed that the osmotic gradient present on the gel's surface determines how quickly gelation occurs. When cations such as mono- or divalent cations are present, the polymer's aqueous solution turns into a transparent gel. Osmotically induced gelation is demonstrated using alginates, a polymer similar to gellan gum.

4.2.2 Chemically induced in-situ gelling system

Three chemical reactions—ionic, enzymatic, and photopolymerization—combine to generate *in-situ* gel systems.

4.2.2.1 Ionic cross linking

Phase changes occur in ion-sensitive polymers such as carrageenan, gellan gum, pectin, and sodium alginate when different ions, primarily K+, Ca2+, and Na+ ions, are present. These polymers belong to the ion-sensitive polymer class. For instance, due of its interaction with a guluronic acid block in alginate chains, alginic acid experiences a phase shift when divalent cations, such as Ca2+, are present.

4.2.2.2 Enzymatic cross-linking

Natural enzyme-catalyzed *in-situ* formation has not been extensively studied, yet this system offers some benefits over alternative methods. An enzymatic process, for instance, functions well under physiological settings without requiring potentially hazardous substances like initiators and monomers.

4.2.3 Stimulus-responsive in-situ gelling system

Minor external changes in the environment that cause physical or chemical changes.

4.2.3.1 pH-triggered mechanisms

Due to the fact that pH may vary in numerous distinct or pathologic bodily regions, including the stomach, gut, endosome, vagina, blood arteries, lysosome, and extracellular sites of tumors, pH is another crucial environment-sensitive parameter for drug delivery. pH-sensitive polymers are those with functional groups that are either acidic or alkaline and react to pH variations. Every pH-responsive polymer has basic or acidic groups that, in reaction to pH variations in the surrounding environment, may either take in or release protons. Polymers containing a high number of ionizable groups are referred to as polyelectrolytes. The primary signal is pH, which may be handled by materials that respond to pH. A change in pH causes the fluid to gel. When the bodily fluid raises the pH to 7.4, the formulation, which is a free-running solution at pH 4.4, coagulates. Polyethylene glycol and polyvinyl acetate, two derivatives of cellulose, are the polymers that exhibit pH-induced gelation. As weakly acidic groups are present in the polymer, the hydrogel swells more as the external pH rises, but lessens when weakly (basic) groups are present.[23]

4.2.3.2 Temperature induced in situ gel system

The stimulus that is most frequently employed in polymer systems that are sensitive to the environment. Not only temperature change is very simple to control, but it is also readily used in both *in vitro* and *in vivo* settings. When in contact with body fluids, these *in situ* gelling systems undergo a temperature rise, becoming liquid at 20˚-25˚C and gelling further at 35˚-37˚C. Temperature-induced gelation is seen in polymers such as xyloglucan, methylcellulose, HPMC, poloxamers, and pluronics.[24]

4.2.4 In situ formation based on the physical mechanism

4.2.4.1 Diffusion

This method involves the diffusion of the solvent into the surrounding tissue from a polymer solution and leads to precipitation or solidification of the polymer matrix. N-methyl pyrrolidone (NMP) solvent is beneficial for this type of system.

4.2.4.2 Swelling

In situ formation can also occur when water is absorbed by the material from the surrounding environment and expands to occur in desired space. The substance like myverol 18-99 (glycerol monooleate), which contain polar lipid that swells in water to make lyotropic liquid crystalline phase structures. It has some bioadhesive properties and may be degraded *in-vivo* by enzymatic action.[25]

5. METHODS OF FORMULATION OF *IN SITU* GEL

5.1 Cold Method

Using this approach, the medication is mixed with enough double-distilled water and refrigerated overnight at 4°C. Next, a gradual addition of the *in situ* gelling polymers is made while stirring. After a clear solution forms, the dispersion is refrigerated until the volume is adjusted with distilled water. When using poloxamer, chitosan, or carbopol as a gelling polymer, this approach is selected. Because the solubility of the polypropylene oxide chain in poloxamer decreases at high temperatures, causing precipitation or salting-out of a polymer, the polymeric dispersion of poloxamer is in solution at lower temperatures and transforms into a gel at higher nasal temperatures. In a similar vein, because of its hydrophobicity, chitosan similarly needs a low temperature to stay in solution at ambient temperature.[26]

5.2 Hot Method

When pectin or gellan gum is utilized as a gelling polymer, this technique is applied. Gellan chains dissolve in water at high temperatures, take on a random-coil conformation with great segmental mobility, and eventually stay in solution at even higher temperatures. In the presence of ions such as K^+ or Ca^{2+}, a phase shift takes place on a cooling gellan gum solution. In a similar vein, pectin's demethoxylation, which aids in the substance's solution production or dissolution, likewise needs a high temperature.[27]

6. CHARECTERIZATION OF NASAL *IN SITU* GEL

6.1 Clarity

Examining the *in situ* gel beneath a black and white backdrop allows one to determine its clarity.

6.2 Gelling Time and Sol-Gel Transition Temperature

The sol-gel transition temperature and pH should be identified for *in situ* gel-forming systems. The amount of time needed for the *in situ* gelling system to detect gelation for the first time is known as the gelling time. For *in situ* gelling at body temperature, thermosensitive *in situ* gel should be examined.

6.3 Gelling Capacity

To determine the gelling capability of an ophthalmic product, mix *in situ* gel with simulated nasal fluid at a ratio of 25:7, meaning that 25µl of nasal fluid in the nostril is equal to 7µl. By timing the amount of time it takes for the produced gel to dissolve, one may visually evaluate the gelation.

6.4 Viscosity

Viscosity and rheological properties may be measured with a variety of viscometers, such as the Brookfield, cone, and plate viscometers, in solution or in a gel made with artificial tissue fluid.

6.5 Drug Content

In a 10 ml volumetric flask, about 1 ml of the produced solution is added until it reaches 10 ml, and then it is diluted with 10 ml of distilled water. Once more, 1 milliliter of this solution was diluted with 10 millilitres of distilled water. Solutions that have been prepared at certain wavelengths are examined using UV visible spectroscopy.

6.6 *In vitro* Drug Release Studies

The dialysis membrane is used in the drug release experiments for *in situ* formulations. The two compartments that comprise the cell are the donor compartment and the receptor compartment. The cellulose membrane aids in the separation of the two cells. The donor compartment is filled with the formulation. At specific intervals, a portion of the receptor solution can be removed and replaced with new media. An analytical approach is used to assess the drug release from this receptor solution.

6.7 Examination for Sterility

As per the IP 1996, sterility testing is performed. The formulation should be incubated for at least 14 days at 30-35˚C in soyabean casein digest medium to detect fungal growth and for at least 14 days at 20–25˚C in fluid thioglycolate medium to detect bacterial growth.

6.8 Studies on Accelerated Stability

In accordance with ICH state criteria, formulation is substituted in amber-colored vials and sealed with aluminum foil for short-term accelerated stability at 40˚±20˚C and 75±5% RH.

6.9 pH of The Gel

Using a pH meter the *in-situ* nasal gel's pH is determined.

6.10 Measurement of Gelation Time

2 ml of formulation gel is taken in a test tube and kept in an oven at 37°C temperature. At specific time gelation of *in situ* gel is examined.

7. CONCLUSION

Intranasal mucosal administration, which targets the brain without the need for a needle and is non-invasive since it crosses the blood-brain barrier and avoid hepatic first-pass metabolism. Benefits of this approach include improved patient compliance and comfort, limited exposure, and fewer side effects. It also permits direct medication administration to the central nervous system (CNS) via the olfactory route through the mucosa. The potential for intranasal formulations to reach the market is predictable. There are restrictions on the use of the intranasal route for medication administration, despite the nasal mucosa's ability to transport pharmaceuticals with controlled release. The mucoadhesive polymeric system is utilized to lessen these restrictions. First, a controlled substance, the *in-situ* gelling mechanism, in this instance, provides patient comfort, which is the main emphasis of delivery. Other benefits of *in-situ* gels include medication release that is extended or maintained. The literature has reported remarkable and innovative research conducted over the last few decades on pH-induced, temperature-sensitive, and ion-induced gel-forming formulations. *In-situ* nasal gels may be further enhanced and made even better as drug delivery systems by using high-quality, biodegradable, biocompatible, and water-soluble polymers in their formulation.

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