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In-situ gel as an alternative approaches for intranasal drug delivery system

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ABSTRACT: One of the most attractive and complex issues that pharmaceutical scientists have is intranasal administration. The traditional nasal drug delivery methods, which include ointments, suspensions, and solutions, have shortcomings such limited permeability, short nasal cavity residence times, and difficult administration. In situ nasal gel systems are a captivating polymeric system that occurs as passing aqueous solution before oversight and goes through phase transition to form a rigid gel in a physiological environment. Profiting from its advantages of having a solution and a gel, a substantial amount of in situ nasal gel systems produced by temperature, pH, and ions have been designed for application in intranasal drug delivery in recent years. Drugs are better retained in the nasal cavity by in situ gel-forming methods, and some of them even exhibit the ability to improve permeability. This review article deals with gelling technicians alongside the other advantageous aspects of the in situ gel-forming systems utilized for intranasal drugs delivery.

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INTRODUCTION:

A substance that is in between a solid and a liquid is called a gel. The solid component composed of a three dimensional network of linked molecules or aggregates immobilizes the liquid continuous phase. Another way to classify gels is by the type of bonds that comprise the three-dimensional solid network. Physical gels are produced by Van-Der Waals Forces, hydrogen bonds, and electrostatic interactions, chemical gels are produced by strong covalent bonds [1].

An increasing variety of medicines are available for systemic and local administration through the nasal

route, making it a significant medication delivery method. A novel dose form is an in-situ gel. Recently, *in situ* gel has been used to provide nasal medications. 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 to prolong the duration of contact between the medication and the site of absorption and to gradually release the medication within the nostrils [2].

A gel is a condition halfway between liquid and solid. It is made up of long polymer molecules that are mechanically cross-linked, trapping liquid molecules inside a three-dimensional network that has been swelled by a solvent. Before injection, the in-situ gelling system is a liquid aqueous solution, and it transforms into a gel at physiological conditions. In-situ gel has remarkable stability, repeatable extended and prolonged drug release, and dependable medicine amounts, rendering it a more precise method [1].

Drug distribution using *in situ* gel can occur through a variety of channels, including oral, ophthalmic, vaginal, rectal, intravenous, and intraperitoneal. Cross-linking of the polymer chain, which can be achieved by either non-covalent (physical cross linking) or covalent (chemical) bond creation, is what causes gelatin. Different mechanisms exist that lead to the formation of in-situ gels. These mechanisms include those that rely on chemical reactions, temperature changes, and pH-triggered systems, as well as those that depend on physiologic stimuli, physical changes in biomaterials, such as solvent exchange and swelling, and UV-radiation, ionic cross linking, and ion-activated systems. No organic solvents, copolymerization agents, or external triggers are required for gelation in this system.

Since proteins and peptides are susceptible to gastrointestinal protease, they are typically administered intravenously. By targeting delivery through the vaginal, rectal, and nasal mucosa, as well as avoiding the hepatic first-pass metabolism, to provide targeted distribution, in-situ gel formulation is used [1].

IN SITU GEL:

In situ is a Latin phrase that means in position" or "in its original place." The creation of continuous and regulated medication delivery systems has received more attention throughout the last 30 years. Many studies have been conducted on the design of polymeric systems, like in situ gels. Drug delivery methods using in situ gel formation are characterized by a liquid formulation that, upon administration, forms a solid or semisolid depot. Systems that transition to a gel phase when subjected to physiological circumstances are known as in situ activated gel forming systems [1-5].

The first time this novel idea of creating a gel *in situ* was proposed in the early 1980s. Cross-linking of polymer chains results in gelatin, which can be done chemically or physically by forming non-covalent bonds or covalent bonds. *In situ*, gel can be administered orally, ocularly, rectally, vaginally, injectable or intraperitoneally. Gel is the intermediate stage between liquid and solid. It is made up of three-dimensional, solvent-swollen networks of long polymer molecules that are physically cross linked. Liquid molecules are trapped within these networks. Before injection, this system is an aqueous liquid solution, and under physiological circumstances, it becomes a gel. The *in situ* gel is more precise due to its biocompatible nature, remarkable stability, and consistent amounts of medicine released over an extended period [2-4].

In situ gel medication administration can occur through a variety of channels, including oral, ophthalmic, vaginal, rectal, intravenous, and intraperitoneal. *In situ* gel has been utilized recently as a new dosage form for the delivery of nasal medications. Nasal *in-situ* gels are applied as low-viscosity solutions into the nasal cavity, as opposed to conventional liquid nasal formulations. The polymer changes its structure when it comes into touch with the nasal mucosa, creating a gel. This allows the medication to be released gradually and continuously, extending the duration of contact between the medication and the cavity's absorptive sites. It is particularly helpful for treatments that are taken regularly. A temperature change, a change in pH, or the presence of cations can all cause the phase transition [1].

Important of *in situ* gel [4-6]:

- The *in situ* formation of polymeric delivery methods facilitates administration with ease.
- Decreased frequency of delivery.
- Enhanced patient comfort and compliance.
- The nasolacrimal duct drains drugs, however, this reduces their systemic absorption, which might lead to certain unwanted side effects.
- Extended duration of nasal retention.

Principle of *in situ* gel:

The *in situ* gelling method for solid nasal formulations is based on the notion that, upon administration, the nasal formulations take in the moisture from the nose and solidify into a gel inside the cavity. By forming nasal gel inside the cavity, the sense of a foreign body can be avoided. Because the gel is bioadhesive, it sticks to the nasal mucosa. It functions as a matrix that controls release, serving as a continuous medication delivery mechanism in the process. The bottom layer of mucus in the nose travels surrounding the cilia, moving ahead during the propulsion phase and backwards during the preparation phase. The cilia extremities scrape the top layer of mucus during the propulsion phase, approximately 0.5 mm through. Then ciliary activity zones appear at different intervals. Because Cilia are positioned rearward, any obstructions during the propulsion phase may be effectively removed. Following gel formation, there is either disintegration or mucociliary removal to the nasopharynx. Therefore, after the dosage form has run out of medication, there is no need to remove it [4-6].

Properties of *in-situ* gel [4-8]:

- It ought to stay put for a long time.
- It must have a low viscosity.
- Free-flowing allows for reproducible delivery to the nasal cavity.
- The nasal in-situ gel follows the phase change process and shear stresses in the nasal cavity wall.

Delivery of *in situ* Gel:

***Therapeutic considerations*:**

The nose is an essential organ for breathing, but it may also be used to administer pharmaceuticals, making it easier to provide dosages that are beneficial for different medications. Aside from self-administration, using the nose to administer drugs allows for quick and high levels of absorption. It works well for administering medications to areas within the central, peripheral, and whole nervous systems. Considering variables including the patient group, dose frequency, and the medicinal goal (local vs systemic), the mode of administration selection is critical for therapeutic outcomes. The recommended method of administration is frequent intranasal delivery [3,7-10].

***Local delivery*:**

The logical choice for medicine delivery for the prevention of common nose disorders is intranasal administration. Antihistamines and corticoids are commonly used to treat the symptoms of colds. In this case, the intranasal route is the better way to administer medication since it has fewer adverse effects and offers immediate treatment [3, 11-13].

***Vaccine delivery*:**

The nasal mucosa are exposed to antigens as a means of immunization. Using an appropriate antigen in conjunction with a powerful adjuvant directed against the lymphoid tissue associated with the nose can elicit humoral and cellular immune responses. This approach may prove to be highly effective in accelerating the mass vaccination process, particularly in children and/or areas experiencing disasters or developmental issues. Both the systemic and local development of immunity can be promoted by intranasal immunization [3, 14-15].

***Systemic delivery*:**

In comparison to oral and intravascular methods, intranasal administration is a more effective technique to deliver drugs systematically. As a result, the number of drugs developed for nasal administration that have systemic effects has grown dramatically.

***Nasal Anatomy and Physiology*:**

It is critical to comprehend the nose's architecture and physiology and how it connects to the features of the delivery method being utilized shown in Fig 1.

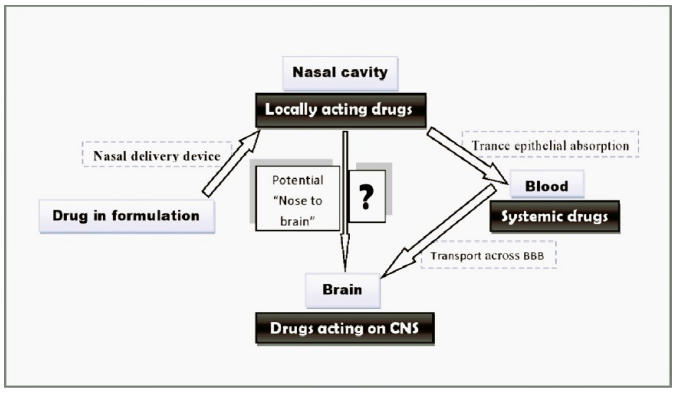

Fig 1. Systemic circulation from the nose to the brain.

In humans, the primary purposes of the nasal cavity in other animal species are breathing and smell. Once the air is breathed and has had time to filter, heat, and humidify before reaching the lowest airways, it also has a significant defensive function. An adult's nasal cavity has a surface area of around 150 cm and a total capacity of 15 to 20 ml. The septum divides the nose into two nasal chambers. Each cavity has a surface area of roughly 75 cm and a capacity of approximately 7.5 ml.

In children, the pH of mucosal secretions fluctuates between 5.0 and 6.7, whereas in adults, it ranges from 5.5 to 6.5. A layer of mucus covers the nasal tube epithelium, and this layer is replaced every ten to fifteen minutes. Every 20 min, particles are cleared from the nose by mucus moving at a pace of 5 to 6 mm/min^2.

Since it can be delivered directly to the central nervous system with no first-pass metabolism is practically painless, noninvasive, and suitable for self-medication, the nasal mucosa has emerged as a recognized site of Administration for systemic medication delivery in recent decades and is now preferred over parenteral medication. Pharmacokinetically, because nasal membranes have a highly permeable nature and a rich vasculature, intranasal delivery avoids first-pass elimination and allows rapid drug absorption [2].

Furthermore, drugs that cannot be taken orally may be able to reach the systemic circulation through the nasal cavity. They undergo extensive first-pass metabolism by the liver, breakdown in the gastrointestinal fluids, or digestion in the gastrointestinal tract wall during their first circuit of circulation. A direct channel from the nose to the brain may offer a more quick and focused therapeutic impact in the treatment of local illnesses such as allergic rhinitis, pain, and centrally acting drugs, for which a large number of nasal medicine products now on the market are advised. In solution, a wide variety of low-molecular-weight (<300Da) non-polar drugs easily pass through the nasal epithelium [2-8].

One proposed process of absorption makes use of aqueous channels. Similar to the gastrointestinal tract, molecules having a molecular weight greater than 300 Da have difficulties being absorbed. An extra barrier is provided by the nasal epithelium because of mucociliary clearance. Absorption enhancers are used to get over this obstacle by making it easier for drugs to pass through the nasal membrane. This improvement may be brought about by the medicine being more soluble and stable, or it might be brought about by changing the mucus layer's characteristics, such as by making tight connections between cells or making the membrane more fluid [2-8].

Many nasal drug delivery methods for the administration of high molecular weight drugs are now under various phases of development. Given the variety of materials being considered, the physical and chemical properties of medications, and the many target regions in the body, it seems unlikely that a universal nasal drug delivery device would be feasible. A delivery system's formulation liquid, powder, gel, microsphere, liposome, or nanoparticle also affects how effective it is [2-8].

There are three distinct areas in each section:

***Respiratory regions*:**

The nasal respiratory region takes up the majority of the nasal cavity, also known as the conchae (Fig 2). The respiratory epithelium is made up of four types of cells: basal cells, goblet cells, non-ciliated cells, and ciliated columnar cells. The respiratory region has three nasal turbinates superior, middle, and inferior, which emerge from the lateral walls of each nasal cavity. The nasal respiratory mucosa is regarded as the most important site for systemic drug delivery [5].

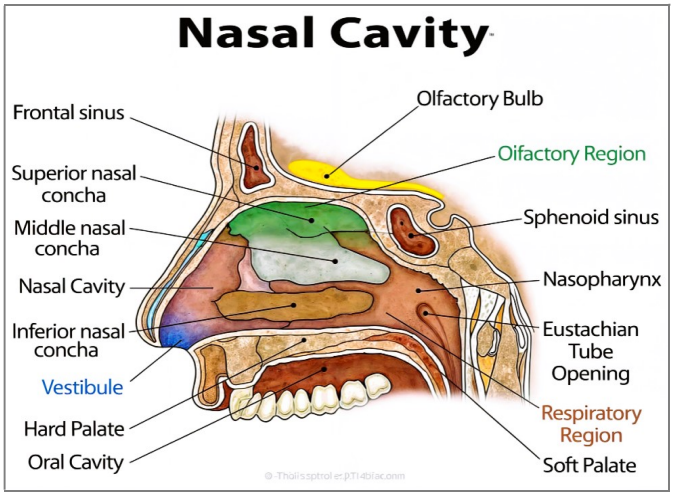

Fig 2. The nasal cavity's anatomy.

***Vestibular region*:**

The nasal vestibule, which is located directly within the nostrils and makes up the majority of the anterior nasal cavity is around 0.6 cm. There are several layers covering this area of the nose. The squamous, keratinized epithelium with sebaceous glands is responsible for eliminating airborne contaminants. In the context of medication absorption, it is seen as less significant in the three areas [5-7].

***Olfactory region*:**

The olfactory region, which has a surface area of around 10 cm^2, is situated on the nasal cavity's roof and extends briefly down the septum and lateral wall, and it is essential for the delivery of medications to the brain and CSF. There are three possible entry points for the medication into the brain when it is taken by nasal route. The first is the systemic route, which allows a medicine to enter the bloodstream and then penetrate the blood-brain barrier to enter the brain (particularly for lipophilic drugs). The medication is delivered directly from the

nasal cavity to the central nervous system (CNS) via the trigeminal neural pathway and the olfactory area. The medications pass the olfactory membrane and enter the central nervous system (CNS) by a separate route. The first route entails the medication being directly transferred to the olfactory epithelium's main neurons, where it is then transported via intracellular axonal transport to the olfactory bulb. From there, it may then be distributed to further brain regions. The second process is dependent on the medication entering the CNS after permeating the olfactory sustentacular epithelium cells via transcellular or Paracellular pathways. The last one uses olfactory neurons' pinocytosis [5-8]. The regions are shown in Fig 3.

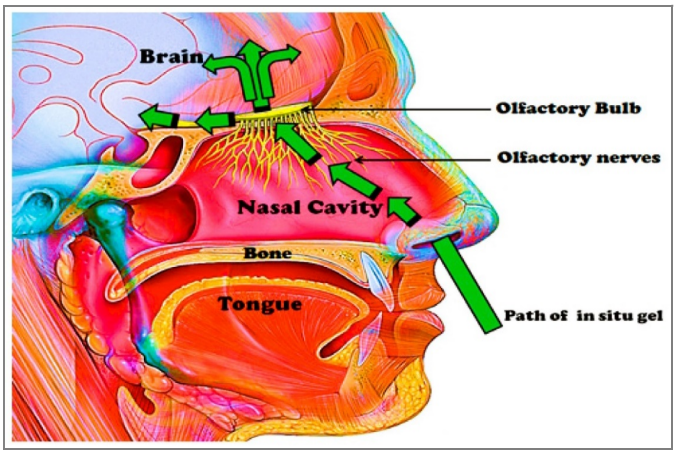

Fig 3. Position of the olfactory bulb concerning the brain and nasal cavity.

It also performs various physiological activities, as listed below [5]:

- This produces the mucosa and keeps it in good structural and enzymatic condition.
- Mucus can retain water.
- On the surface, this displays electric behavior.
- It facilitates effective heat transmission.
- It serves as glue and transports particulate materials to thenostrils.

Mechanism of drug absorption:

Drugs taken by the nasal route for systemic or central nervous system effects are absorbed when they cross the mucous membranes and epithelial barrier and arrive to enter the central nervous system directly. Drug absorption for a systemic impact is thought to occur in the respiratory area, which includes the nasal septum and turbinate. Adjacent to the respiratory area, the olfactory area is the primary place from which the medication can be directly absorbed into the brain for central nervous system effects. When a medication is administered intravenously, it can travel straight to the brain through either the systemic circulation (blood) or the olfactory area. Via the trigeminal neural circuit or the brain, which is how a medication enters the brain and passes through to the CSF (cerebrospinal fluid). Therefore, the nasal mucosa's olfactory region. It provides a direct channel of communication between the nose and the brain and may be utilized to target CNS-acting medication molecules in order to treat diseases like depression, migraines, schizophrenia, epilepsy, brain tumors', pain, and Alzheimer's and Parkinson's disease [5].

].The mucus layer is where the absorbed drugs must travel from the nasal cavity. This is the beginning of absorption. The medication with little larger, charged drugs has a harder time getting through this mucous layer than smaller ones. The primary protein in mucus, known as mucin, tends to adhere to the solute and obstruct diffusion. Environmental variations such as pH and temperature might cause further structural changes in the mucous layer. The method of drug absorption via the mucosa is distinct [5-10].

Table 1. Mechanism by which drugs penetrate through mucous [5].

Para-cellular process	Transcellular process
➢ Watery mode of transportation. ➢ The procedure takes place inside the cell and is carried out by a vesicle carrier. ➢ This path is passive and moves slowly. ➢ Well suitable for hydrophilic medications. ➢ The molecular weight of water-soluble substances and intranasal absorption have an inverse log-log relationship. ➢ It are shown that medications having molecular weights larger than 1000 Daltons have low bioavailability.	➢ Lipoidal transport pathway. ➢ Drugs can also pass through narrow junction openings via carrier-mediated transport, an active transport pathway, to cross cell membranes. ➢ It is a method of delivering lipophilic medications that exhibit rate dependency based on lipophilicity. ➢ For instance, the natural biopolymer chitosan helps to deliver drugs by loosening the tight junctions that separate epithelial cells.

Among them, comprise transcellular (fundamental diffusion via the membrane) and paracellular transport (vesicle carriers moving across cells during transcytosis). Absorbable drugs have a short half-life in the cavities and may be digested before they enter the bloodstream. Drug transport through the membrane has

been accomplished by a variety of methods, including transfer, transcytosis, absorption, and efflux carried out by carriers, as well as passive diffusion (paracellular and transcellular) nasal epithelium. The two pathways, which are often employed in drug transport across the nasal epithelium, are compared in Table 1 in several significant ways.

Properties of Drugs used for nasal drug delivery system:

- Log P < 5, molecular weight < 500 Da.
- Aqueous solubility: less than 50 mg/ml.
- Dose potency: less than 5 mg/dose/puff per nostril.
- Drug in solution: osmolality less than 500 osm/kg, pH of about 5.5.
- No drug-induced nasal discomfort.
- No harmful metabolites.
- Volume 25 to 125 µl each nostril.

Advantages of *in situ* gel [7]:

- Increasing patient ease and compliance.
- Quick absorption and the start of the pharmacological effect.
- Good penetration.
- Medication is sent directly to the CNS system.
- Keeps away from a hostile environment.
- A low dosage is necessary.
- Decreased chance of spreading infectious diseases.
- The nasal mucosa is not made of the keratinized stratum corneum in contrast to the skin.
- The amount and rate of absorption, together with the temporal patterns of plasma concentration vs time, are equivalent to intravenous delivery.
- There are several nasal medication delivery methods available for simple, painless, noninvasive administration.

Disadvantages of *in situ* gel [7]:

- High levels of fluids are needed.
- The sol form of the medicine is more prone to deterioration.
- Chemical breakdown may cause stability concerns.
- Eating and drinking may be limited for a few hours after medicine is administered.

Ideal qualities of polymers for *in situ* gel production [7]:

- It should be possible for the polymer to stick to the mucosal membrane.
- It ought to work well together and not have any harmful side effects.
- It ought to behave in a pseudoplastic manner.
- As the shear rate increases, the polymer ought to have the ability to reduce viscosity.
- Preferred polymer's pseudoplastic properties.
- It is preferable to have good optical clarity and tolerance.
- It ought to affect the way tears behave.

Table 2. Limitations of Intranasal Delivery.

Limitation	Factors
Low bioavailability is indicated by a reduced nasal absorption capability.	Owing to pathologic diseases like allergies or colds, which can drastically change the nasal bioavailability. • Insufficient water solubility.
Occasionally, the medications irritate the nasal mucosa and permanently harm the cilia.	Due to the ingredients that were added in dose forms.
The permeability of drugs is influenced by defence mechanisms, including mucociliary clearance.	An enzyme barrier affects the drug's permeability.
Cause the nasal membrane to rupture and disintegrate.	Owing to the elevated levels of absorption enhancers.
It is not possible to provide high molecular weight molecules (mass cut off = 1 kDa).	There is not enough room in the nasal cavity for the 25–200 ml volume that may be disseminated.
An administration that is irreversible.	If the medication is given and cannot be withdrawn.

Ideal medication for nasal drug delivery [7]:

- The medication should not cause the nasal mucosa to get irritated.
- The medication should not have any negative effects.
- There should not be any metabolites in the medication.
- The medication must not include any dangerous or disagreeable smells.
- The medication should not exceed a dosage of 25 mg.
- The medication needs to have the right nasal absorption characteristics.
- Adequate clinical justification for a nasal delivery system.
- Adequately steady attribute.

Polymer used in the *in-situ* gel [8-15]l:

- The polymers and byproducts of their breakdown ust be safe and incapable of being absorbed by the digestive system.
- It should have some site-specificity and stick to the wet tissue immediately.
- No mucous membrane irritation should occur from it.
- It needs to have a large safety buffer on a local and systemic level.
- To maintain the produced dosage form's competitiveness, the polymer value should not be excessively high.

Different polymers are employed in the *in-situ* gelling system preparation process:

***Carbopol*:**

Sol-gel transition is observed by Carbopol in aqueous solutions when the pH rises above its pKa. When the polymer is dissolved in water, its acidic carboxyl groups start to uncoil and establish a framework of flexible coils. Certain carboxyl groups on the polymer dissolve to create a flexible coil shape when exposed to acidic environments. Negative charges are produced along the polymer backbone when the carboxyl groups ionize in an alkaline substrate. Polymer swelling and gel formation are the outcome of the anionic group's electrostatic repulsion, which uncoils and expands the molecule. By screening the carboxyl groups with the cations, further carbopol addition thins the gel by reducing electrostatic repulsion [15-18].

***Poloxamer*:**

Poloxamer is a water-soluble tri-block copolymer with an ABA structure composed of two cores of polyethene oxide and one core of polypropylene oxide. Another name for poloxamer is pluronic. Poloxamer extends the drug's residence duration and has strong thermal setting properties. It has both solubilizing and gelling properties. a transparent, colourless gel produced by poloxamer. The distribution and ratio of hydrophilic to hydrophobic chains determine the molecular weight and gelling characteristics of the material. It is made up of polyethene oxide around a core of polypropylene oxide. It behaves as a viscous liquid at 25 ºC and changes into a translucent gel at 37 ºC. It forms a small micellar subunit in solution, and at lower temperatures, swelling results from temperature and viscosity changes that form a vast cross-linked micellar network [15-19].

***Xyloglucan*:**

Tamarind gum, also known as xyloglucan, is a polymer that is extracted from the seed's endosperm. Xyloglucan is composed of three distinct oligomers, such as distinguishing between pentasaccharide, pentasaccharide, and monosaccharide based on the quantity of galactose side chains. Oral, rectal, and ocular medication administration is its primary use because of its non-toxic, biodegradable, and biocompatible qualities. For example, when the polymer is heated to refrigerator temperature or chilled to a higher degree, gelation occurs [20-23].

***Gellan gum*:**

The microorganism *Sphingomonas elodea* secretes gellan gum, an anionic heteropolysaccharide. It is made up of glucuronic acid, rhamnose, and glucose that are joined to acquire a unit of tetrasaccharide. Deacetylated gellan gum, or gelrite, is produced by subjecting gellan gum to an alkali solution, which eliminates the acetyl group from the molecule. The presence of calcium ions causes gelrite to develop as a result of installation. To create three-dimensional networks, the gelation process involves the production of double-helical junction zones, which are followed by the aggregation of double-helical segments via complexation with cations and hydrogen bonding with water. Gellan gum is used as a stabilizing and suspending agent in the food business [24-29].

***Xanthum gum*:**

High molecular weight extracellular polysaccharide, or xanthan gum, is created when the gram-negative bacteria Xanthomonascampestris ferments. This naturally occurring cellulose derivative's main structural components are β-D-glucose residues, which serve as the cellulosic backbone, and β-D-mannose trisaccharide side chains.ˌ-D-mannose linked to β-D-glucuronic acid by alternating glucose residues in the main chain. The gum called xanthan gum dissolves in both hot and cold water and in alkaline and acidic conditions. High stability is observed in alkaline conditions [26].

HPMC (Hydroxypropyl Methylcellulose):

The glucan chain that makes up cellulose contains repeating units of β-(1, 4)-D-glucopyranose. Temperature-sensitive sol-gel phase transition is shown by some natural polymers, such as HPMC, MC, and EC. When the temperature drops, cellulose material will become more viscous, and when the temperature rises, its derivatives, such as HPMC and MC, will also become

more viscous. MC is a naturally occurring polymer consisting of native cellulose with a chain that alternates between methyl substitution groups. The solution is liquid at low temperatures (300 °C), while gelation occurs at higher temperatures (40 to 500 °C) [22-27].

Evaluation of *in situ* Nasal gel:

***Gel strength*:**

The samples (50 g) are put into a graduated cylinder measuring 100 ml. The formulations were gelled by placing them in a thermostat set to 37 °C. The time it took for a 35 g weight to sink 5 cm in the gel is used to gauge the gel's strength [14-18].

***Spreadability*:**

Spreadability is measured using a 10 × 4 cm rectangular glass slide. The sheep's nasal mucosa is attached to the slide's surface from the serosal side using a thread. The slide is kept at 37 degrees Celsius in a hot air oven, and one drop of gel is placed on the mucosa at a 120 ºC angle. A liquid gel drop's spreadability is calculated as a function of its travel distance before gelatin. Three measurements were averaged out [14].

***The viscosity of solution*:**

The viscosity of the *in situ* gel systems are measured using the Brookfield viscometer DV-II+Pro, which are attached to the S-94 spindle. The gel compositions that were made were put into the beaker. The temperatures are maintained at 37 ± 0.5 °C while the spindle is plunged perpendicularly into the gel at a speed of 1.000 rpm. The viscosity is measured during the cooling process of the system. Three measurements were made for each [14].

Drug content:

A 10 ml volumetric flask is filled with about 1 ml of the produced solution, diluted with 10 ml of distilled water, and then sealed. Once more, 1 milliliter of this solution is diluted with 10 milliliters of distilled water. Tests are conducted on prepared solutions at certain wavelengths using UV-visible spectroscopy [14].

***Determination of pH*:**

After 1 ml of the generated gels was added to a 10 ml volumetric flask, the mixture is diluted with distilled water. We measured the pH of the resulting solution using a digital pH meter that had been calibrated using phosphate buffers at pH 4 and pH 7 [11-14].

***Gelling temperature*:**

The term "gelling temperature" describes the temperature at which, after tilting the test tubes 90 degrees, the formulation's meniscus would no longer move. The methods of Miller and Donovan are applied to ascertain the gelatin experiments. By setting the test tube, which contained an adequate amount of the produced solutions, in a water bath at 4 °C, the gelling temperature is ascertained. The water bath's temperature is gradually raised every 2 min at a steady pace of 1 ºC [15-26].

Gelling time:

The methods outlined by Miller and Donovan were used to calculate the gelling time of formulations. The delivery systems are present in a sol state before administration; however, they go through a gelatin process after that to become gels. The initial discovery of gelatin is noted as gelling time. By adding 2 ml of the obtained formulation to a test tube (10 ml) with a diameter of 1.0 cm, the sol-gel transition temperature (Tsol-gel) of the prepared *in situ* gel formulations are measured. The tube is kept in a 37 °C circulating water bath after being parafilm-sealed. Equilibration is given 10 min after each temperature setting. To monitor the sample's condition and to finally insert the test tube horizontally and examine the gelatin [26-40].

CONCLUSION:

The current analysis finds that one of the greatest new drug delivery methods that have evolved is the "*in situ* gel" technology, which facilitates continuous and more comfortable and compliant patients, regulated medication release, with *in situ* nasal gel formation, natural and synthetic polymers can be used in application of intranasal drug delivery. Research into the *in situ* nasal gel system has the potential to provide cutting-edge technologies for medicine administration.

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