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In Situ Gelling Systems for Nasal Drug Delivery: Formulation Strategies and Therapeutic Applications

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Abstract

Intranasal delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. Nasal delivery is an alternative to oral or parenteral administration due to certain limitations such as absorption of the drug, drug targeting to particular organs can cause a problem for administration through oral route. The nasal route has also been successfully used for bypassing the blood-brain barrier and afterword delivering drug molecules to the central nervous system. Also, lag time related to oral drug delivery is reduced by this route and offers noninvasiveness, self-medication, patient comfort, and patient compliance. Extend drug delivery can be attained by different new dosage forms like in situ gel. In situ formulations are drug delivery systems. In situ gel-forming systems increase the retention of drugs in the nasal cavity, and some of them also show permeation-enhancing capabilities. This article reviews the in-situ gel-forming systems used for nasal drug delivery and introduces their gelling mechanisms and other favorable features for intranasal delivery. It also describes the release patterns and drug stability of in situ gels as well as their in vivo performances and local safety following nasal administration.

Keywords: Drug Delivery, In situ gel, Nasal Cavity, Nasal Delivery

1.1 Introduction of drug delivery system

drug delivery systems are technical structures that prepare and store drug molecules so they may be delivered to the intended location within the body. A drug delivery system can increase the therapeutic substance's effectiveness, safety, and ability to regulate the drug's rate of absorption in the body. When a drug is consumed, its constituent parts are what give it its physiochemical characteristics and cause the changes in the physiological systems that it affects. Occasionally, a drug's formulation for therapeutic use or device may use for delivery of drug at targeted site. If a drug is integrated into a device to prevent problems, or if the device is inserted into the body for a purpose other than drug delivery, such as a physical modality that has a therapeutic impact. There are several ways that drugs can enter the body, including the oral, buccal, and sublingual routes; other routes include the nasal, ocular, transdermal, subcutaneous, transvaginal, and intravesical. Patients were provided the oral route of administration due to its benefits, which include patient compliance and ease of administration, despite its difficulties with absorption via the gastrointestinal tract. Transdermal patches can sometimes be used to deliver drugs to specific sites and increase bioavailability [1].

The nasal drug delivery technique has attracted more interest in the past several years. The nasal cavity is a widely accepted and conveniently accessible route. The nasal mucosa has many blood arteries that aid in drug absorption, which in certain cases is nearly as effective as intravenous injections. Both local and systemic drugs distribution are possible with the nasal method of administration [2]. For example, nasal congestion, rhinitis, and associated allergy disorders are commonly treated with localised nasal administration of drugs. Local administration of a wide range of medications is possible, such as corticosteroids, antihistamines, anticholinergics, and vasoconstrictors. More focus has been placed on using the nose as the entrance point into the body to achieve a systemic pharmacological effect in recent years. To accomplish systemic pharmacological activities, a variety of pharmaceutical dosage forms, such as gels, suspensions, emulsions, liposomes, and microparticles, can be utilised. The main purpose of these dosage forms is to take advantage of the quick start of action when used in the nasal route. Additionally, vaccinations such as those for influenza can also be given via the nose [3].

The nasal cavity has several advantages for systemic distribution, including a wide surface area for drug absorption, quick blood drug levels to reach therapeutic levels, especially for lipophilic and low molecular weight medicines, high drug permeability avoiding unfavourable dietary and environmental circumstances, bypassing the first-pass metabolism in the liver, Possibility of direct medication administration via the olfactory nerves to the brain to increase patient compliance [4].

Thermoreversible polymers are used to create a nasal In situ gel that is liquid-like before to nasal delivery and gels upon contact with the nasal mucosa. They are a brand-new state of matter with characteristics that are halfway between solid and liquid. They may be administered as a fluid and solidify in the body at temperatures above the sol-gel transition point. Because the formulation has a longer residence time in the nasal canal, it has the benefit of preventing anterior dosage form leaks and improving nasal bioavailability [5].

1.1.1 Anatomy and physiology of nose

There are two parts to the nose: the external part that is visible and the internal part that lies inside the skull. The outer layer is composed of a mucous membrane-lined, muscle-and skin-covered structure made of hyaline cartilage and bone. The skeletal framework of the external nose is made up of the maxillae, nasal bones, and frontal bone. The lateral nasal cartilages below the nasal bones, the alar cartilages, which form part of the nostril walls, and the septal cartilage, which forms the anterior section of the nasal septum, make up the cartilaginous structure of the external nose. The cartilaginous structure of the external nose is rather flexible since it is made of pliable hyaline cartilage. Two orifices known as the external nares or nostrils are located on the underside of the external nose.

The internal part of the nose is a sizable, muscle- and mucous membrane-lined chamber located in the front section of the skull, superior to the mouth and inferior to the nasal bone. Through two apertures known as the internal nares, the internal nose is joined to the pharynx. The internal nose is also the opening for ducts from the nasolacrimal ducts and paranasal sinuses. The ethmoid bone forms the roof of the internal nose, while the maxillae, lacrimal, palatine, and inferior nasal conchae bones create the lateral walls. The nose has several functions such as, moistening, warming, and filtering incoming air, detecting olfactory smell and modifying speech vibrations as they pass through the large [6].

The nasal cavity is the area that is located inside the internal nose. The vestibule, or front half of the nasal cavity, is bordered by cartilage, whereas the superior part of the nasal cavity is enclosed by bone. The nasal cavity is divided into the right and left sides by a vertical wall called the nasal septum. The maxillae, palatine bones, vomer, and perpendicular plate of the ethmoid make up the remaining half of the septum, which is mostly composed of hyaline cartilage. nasal cavity into the superior, middle, and inferior meatuses, which are a sequence of groove-like channels. The three conchae and the nasal cavity are lined by mucous membrane. Conchae and meatuses are arranged to improve interior nasal surface area and avoid dehydration by capturing water droplets during expiration [7].

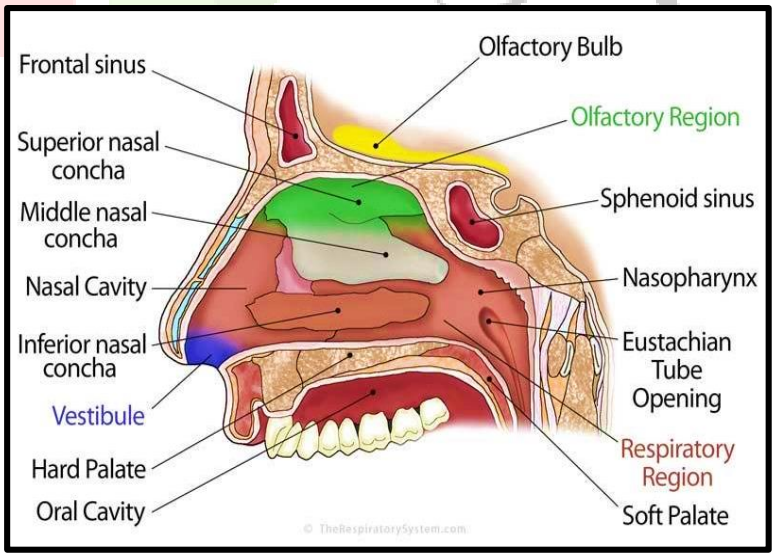

Figure 1.1: Anatomy of Nasal cavity

The olfactory epithelium is a section of the membrane that borders the nasal septum and superior nasal conchae, and it contains the olfactory receptors. below the olfactory epithelium in position. Capillaries and pseudostratified columnar epithelium are present in the mucous membrane. Numerous goblet cells and ciliated columnar cells may be seen in the pseudostratified columnar epithelium of the respiratory system. Blood in the capillaries warms the breathed air as it circulates around the conchae and meatuses. The goblet cells release a mucus that both moisturises the air and collects dust particles. The air is additionally moistened by drainage from the nasolacrimal ducts, which is occasionally aided by paranasal sinus secretions. The cilia push the trapped dust particles and mucus towards the direction of the throat, where they can be spat out or ingested, clearing the respiratory system of the particles [8].

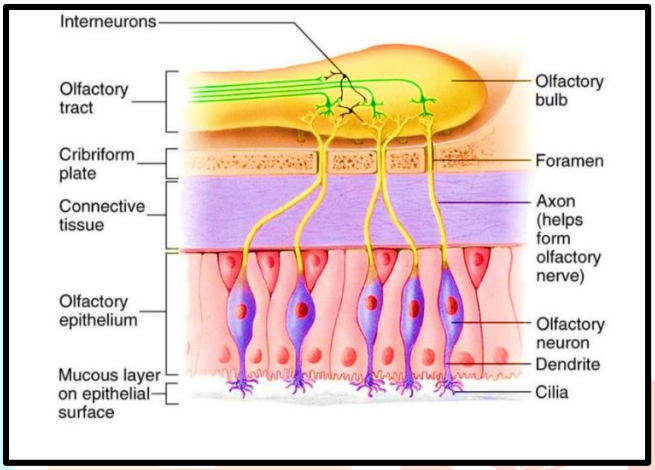

Figure 1.2: Olfactory epithelium

Advantages of nasal drug delivery [9,10]

- It avoids first-pass hepatic metabolism.
- Nasal drug administration can carry drugs that are not taken orally into the systemic circulation.
- It is possible to obtain rapid drug absorption and onset action.
- For smaller drug molecules, nasal bioavailability is good.
- Convenient for patients compared to parenteral route, particularly for those undergoing long-term treatment.
- Nasal delivery is used to provide drugs with low stability in GIT fluids.
- Using an absorption enhancer or another method, it is possible to increase the bioavailability of larger drug molecules.

Limitations [11]

- Local adverse effects and permanent cilia damage on the nasal mucosa are possible due to the drug and other ingredients in the dosage form.
- Uncomfortable for patients in comparison to oral administration methods due to possibilities for nose discomfort.
- The nasal cavity has a lesser surface area for absorption than the GIT.

1.1.2 Nasal route as an application of drug delivery

An intra-nasal route has become a viable method for delivering medications to the brain in recent years. This olfactory route provides the possibility to cross the blood-brain barrier (BBB) and may be used for paracellular, transcellular, or neuronal transport in the transfer of sensory information from the nose to the central nervous system [12]. When administering the stomach route is not practical, the nasal route can serve as a helpful substitute for the oral route in the absorption of drugs. Numerous physicochemical characteristics, such as the drug's solubility, molecular weight, particle size, and acid-base dissociation constant (pKa) and partition coefficient, can affect the amount of the drug is absorbed. Nasal drug administration is typically used to treat nasal cavity-associated disorders such congestion, rhinitis, and related allergy diseases. One can deliver a wide variety of medications locally, such as corticosteroids, antihistamines, anticholinergics, and vasoconstrictors [13].

1.2 Histamine

The body naturally produces a substance called histamine. In reaction to allergens and other foreign substances, it is essential to the immune system. Histamine is secreted by the body in response to allergens from specialised cells known as mast cells. Four different types of receptors H_1, H_2, H_3, and H_4 modify the effects of histamine.

1.2.1 H_1 Histamine receptor [15]

Various allergic reactions due to H_1 Histamine receptor,

- Allergic rhinitis
- Motion sickness
- Bronchitis
- Angioedema
- Nausea

Allergic rhinitis: An inflammation of the nose caused by an overreaction by the immune system to airborne allergens is known as allergic rhinitis, of which the seasonal form is known as hay fever. Hay fever symptoms include stuffy nose, throat, mouth, and eyes, as well as sneezing and nasal congestion.

Bronchitis: An inflammation of the lining of your bronchial passages is called bronchitis. Your lungs receive and release air through these tubes. Bronchitis patients frequently cough up thicker, sometimes coloured mucus. Acute infections of bronchitis can occur quickly, whereas chronic infections occur gradually over time. Acute bronchitis is a common respiratory illness that frequently follows a cold. It normally goes away without any lasting consequences in a week to ten days. A more serious condition known as chronic bronchitis is characterised by a persistent irritation or inflammation of the lining of the bronchial tubes, frequently brought on by smoking.

Motion sickness: Motion sickness is a typical illness that occurs when you are in motion while sitting motionless, such as when you are riding in a car. It occurs when the brain receives contradictory signals from your body, inner ear, and sight. Headache, chilly sweats, and nausea are some of the symptoms. motion sickness may be avoided or its effects can be lessened.

Angioedema: Angioedema is a reaction to a trigger that results in swelling in the dermis, or the layer underneath a mucous membrane, the innermost layer of your skin. Angioedema occurs suddenly and lasts for one or two days. Usually, it affects your eyes and lips. But if angioedema affects your airways, it can become dangerous or even fatal.

Nausea: A nausea attack is a sick feeling in the stomach that gives you a sense that you are about to throw up. This symptom can be brought on by a variety of conditions, such as food poisoning, motion sickness, morning sickness, chemotherapy, gastroenteritis ("stomach flu"), and even strong, unsettling odours. A nausea attack is characterised by discomfort in the upper abdomen, middle chest, or back of the neck.

1.3 Introduction of dosage form

1.3.1 In situ gel:

Gels are a type of material that is intermediate between liquid and solid. It has three-dimensional (3D) solid networks and is soft and stable [16]. Gels blend the fluid's diffusive transport features with the cohesive qualities of solids. Polymer networks are created in gels by the cross-linking of polymer chains, which can be done chemically or physically [17]. Gels are divided into two distinct groups according to the type of bonds they have:

Physical gels: It develops when the gel network is maintained by weak connections such as van der Waals, hydrogen, and electrostatic bonds.

Chemical gels: It develops when the gel network is maintained by strong covalent connections. The network shows the existence of cross-links, which prevent the hydrophilic polymer from dissolving in an aqueous solution [18].

The polymeric chains that make up three-dimensional (3-D) formations are called hydrogels. Thus, they are easily formed into a variety of shapes and sizes. These hydrogels, which belong to the category of hydrophilic preparations, have a great absorbing capacity to switch between liquid-gel and itself [19]. Preformed hydrogels and In situ gels are the other two categories into which hydrogels are divided.

Preformed gels are simple viscous liquids that are unchangeable once administered [20]. A revolutionary approach called "preformed gels" was developed to address some of the particular shortcomings of the In situ gelation system. Preformed gels are superabsorbent cross-linking polymers that may swell up to 200 times their original size and function as a fluid diverting agent to manage compliance [21]. Select for premade gels to get over issues like variations in the composition of the gel, deterioration, and inability to regulate the gelation duration. However, it has an ocular dosage form flaw due to dilution by water, which includes less precise dosing, impaired vision, lacrimation, etc. Prior to being injected into the reservoir, prepared gels are created on the surface. As a result, no gelation happens, and factors such as pH, salinity, temperature, shear rate, multivalent ions, and hydrogen sulphide must be considered [22].

A suspension or solution comes into touch with body fluids or experiences physicochemical changes such as pH, temperature, ionic concentration, UV radiation, the presence of certain molecules or ions, external triggers, etc. it begins to form gel. This is known as an In situ gel. With its sol-to-gel transitioning capabilities, In situ gels are commonly used for sustained drug delivery. It is connected and absorbed in gel form, and it is known to prolong the life of medication in the mucosa by prolonging the drug's release into the body, resulting in a consistent plasma drug profile [23]. As their environment changes, intelligent polymers shift their

physicochemical characteristics. Utilising the changes in physiological individuality has been made possible by recent advancements in In situ gels [24]. less complex, which reduces investment and manufacturing costs from a manufacturing perspective.

Gel formulations are utilised in the discovery phase to increase the local and systemic exposure of possible lead compounds, which is perfect for rapidly and economically developing animal models for a range of situations. In order to create a local or systemic impact of the medication loaded, they can be supplied by a variety of ways. In situ gelling systems can be administered non-parenterally by the oral, ocular, nasal, vaginal, injectable, intraperitoneal, and rectal routes [25].

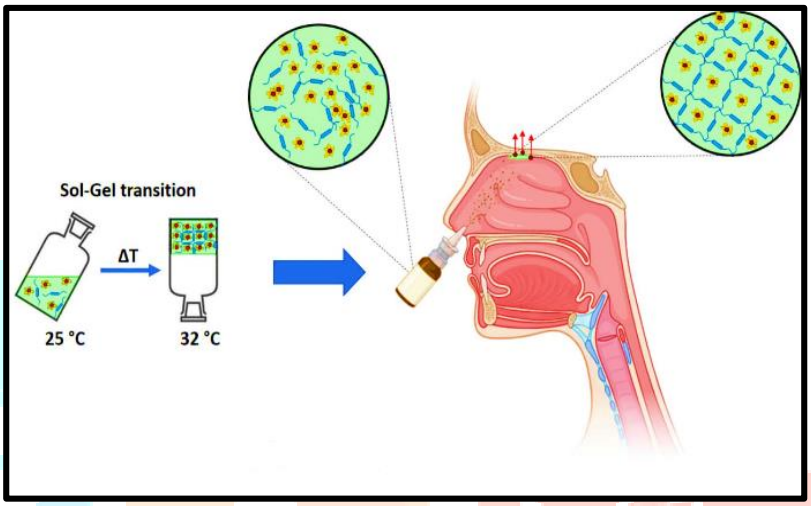

Figure 1.4: Process of In situ gel formation

Significance of In situ gelling system [26,27]

- In situ gel helps for the controlled and sustained release of the drug by its special 'Sol Gel transition.'
- Due to gel formation, there will be more drug interaction and residence duration in the tissue.
- The drug just has to be taken at low doses, and there won't be any adverse effects or drug accumulation.
- The In situ gel method reduces drug waste.
- The physical structure of In situ gel solutions makes them easier to administer, which enhances patient comfort and compliance.
- It facilitates the body's ability to administer drugs less often.
- Notable improvements in a drug's bioavailability and decrease in dose.

Advantages [28,29]

- Natural macromolecules stimulate biological activity and are biocompatible, biodegradable, and biometric materials.
- The drug is delivered controlled and sustained manner.
- Enhanced bioavailability and prevention of the first pass impact.
- Patients who are unconscious might be given In situ gel.
- It can reduce drug toxicity and dosage frequency.
- Improve the comfort and compliance of the patient.
- The "stealth" properties that In situ gels offer in vivo are vital because of their hydrophilicity.
- Application at the site is simple.

- Bio-adhesive In situ gels can be designed to promote drug targeting, particularly across mucous membranes, enabling non-invasive drug delivery.

Disadvantages [30,31]

- Food and drink intake was seen to be restricted for a few hours following the administration of the drug.
- Only drugs with low dosage requirements may be administered.
- The hydrogel could dissolve or be prematurely ejected from certain local locations due to its poor mechanical strength.
- The drug's sol form is prone to disintegration.
- There is possible solubility issues brought on by chemical decomposition.

Applications of In situ gel [32,33]

These In situ polymeric systems can be categorised as shown in the following sections based on the mode of administration.

Nasal drug delivery system

The nasal cavity has become a desirable channel for multi-site targeting in the delivery of a broad range of medications, including vaccines, peptides, proteins, and tiny molecules. For the topical delivery of drugs intended to treat local problems affecting the nose and sinuses, such as sinusitis, allergic or infectious rhinitis, nasal sinusitis, and nasal sinus lesions, the nasal route is a natural alternative. The nose-to-brain administration method ensures that drugs are directly and quickly transported via the olfactory neuroepithelium from the nasal cavity to the central nervous system (CNS). The drug is quickly removed from the nasal cavity because of the self-clearing process, which shortens the time it takes for the drug to cure local ailments of the nose, enter the systemic circulation, or reach the central nervous system. Certain formulations may be delivered conveniently as low viscosity polymeric solutions, and when they come into touch with the mucosa, they gel. Temperature, pH, and ionic strength are three specific physical or chemical stimuli that can cause the sol–gel transition.

Oral drug delivery system

Natural polymers such as pectin, xyloglucan, and gellan gum are used In situ to construct oral medication delivery systems. There have been reports on the possibility of using an oral In situ gelling pectin formulation to distribute paracetamol over time. Pectin's solubility in water eliminates the need for organic solvents in formulations, which is the primary benefit of employing it for these purposes. When taken orally, the stomach's acidic environment releases calcium ions, which cause the gellan nus to gel and create a gel in place. Comparing gellan formulations to the commercial sustained release liquid dosage form, researchers found that theophylline had a higher bioavailability and a prolonged drug release profile in rats and rabbits.

Ocular drug delivery system

Ocular drug delivery is a challenging target with a limited therapeutic response due to the peculiarities of the ocular cavity and its efficient clearance mechanism.

The goal of new generation ophthalmic formulations is to increase the therapeutic effectiveness of medications by making them more readily available for use through the ocular route. Topical administration and gel formation in the conjunctival cul-de-sac enhance long-term therapeutic benefits, lower dosage requirements,

and increase patient compliance by allowing the medicine to be released gradually. Making sure that the polymer solution's viscosity drops as the shear rate increases can help prevent uncomfortable blinking. In addition to being involved in enhancing drug solubility, the In situ gelation technology also plays a role in improving corneal permeability, which is a characteristic of the low bioavailability of the eye, and drug-filled nanoparticles. Longer retention on the ocular surface is achieved by incorporating low-viscosity colloids into semi-solid formulations.

Vaginal drug delivery system

Drugs having both local and systemic effects can also be administered through the vagina. Traditionally, the vaginal route has been used to topically provide antibiotics, hormones, spermicides, and anti-inflammatory medications. Not only that, but the vagina has a lot of blood flow, a big surface area, and the ability to avoid first-pass metabolism, which opens up a vaginal channel for systemic drug delivery. The use of In situ gelling and mucoadhesive formulations is a tactic that has been suggested in recent decades to extend the duration of liquid vaginal formulations' residency at the site of action/absorption.

Rectal drug delivery system

Many different types of medications that are given as liquids, semi-solids like creams and ointments, or solid dose forms like suppositories can all be administered via the rectal route. When placed, traditional suppositories frequently cause discomfort. Moreover, the suppository can occasionally go upward into the colon and is insufficiently retained in one spot within the rectum, allowing the medication to experience the first-pass effect. A recently designed liquid suppository for In situ gelling has a gelling temperature of between 30 and 36^{o} C. To get temperature-sensitive gelling characteristics, poloxamer 407 or poloxamer 188 were utilised. Rectal pathways may be treated using In situ gels.

Intravesical drug delivery system:

Formulations utilising In situ gelling have garnered attention as a potential topical and sustained drug delivery for chemotherapy drugs. Such a system, in the sol form before to delivery, becomes a gel in response to a intratumoral injection. specific stimuli and carefully delivers the medication at the local level. elevated medication levels Maximise antitumor action at the tumour location while minimising harmfulness to the system. Furthermore, the hydrogel's three-dimensional structure guarantees long-term medication release that increases the amount of time that tumours are exposed to chemotherapy drugs.

1.3.2 Basic Components of In situ gel [34]

Sr. no.	Ingredients
1	Drug
2	Thermosensitive polymer
3	pH activated polymer
4	Ion activated polymer
5	Mucoadhesive polymer
6	Preservative agent
7	Isotonic agent

1.3.3 Approaches [35,36]

There are four methods by which biomaterials can be produced into In situ gel. These include: In situ gel formation due to physiological stimuli (Temperature and pH triggered In situ gelling systems), ion-activated system, In situ gel formation due to Physical mechanism (Swelling and Diffusion), In situ gel formation due to Chemical reaction (Ionic, enzymatically cross linking, Photo-polymerization).

a) In situ gel formation due to physiological stimuli

Temperature triggered In situ gelling system

Among environmentally responsive polymer systems used in drug administration, temperature-sensitive polymers have been investigated the most. This is because, in both in vitro and in vivo settings, temperature is a very simple parameter to regulate. The medicine may be released continuously in this kind of gelling system since the gelling of the solution is accomplished by a temperature change. As body warmth is the source of this gelation, external heat application is not necessary. When these gels come into contact with bodily fluids, their liquid state at 25–30°C will change to a gel state as a result of the temperature increase to 35–37°C.

The thermosensitive sol-gel polymeric system is developed using three primary techniques. As a result, they fall under: Thermosensibly negative, contracting when heated, positively thermosensible, contracting in response to cooling Gel that can reverse heat.

Gels that are sensitive to negative temperatures have a lower critical solution temperature (LCST) and collapse when heated over this point. For this, low critical temperature (LCST) polymers are utilised, which are able to shift between ambient and physiological temperatures. One of the most studied polymers with a practical LCST transition is poly(N-isopropylacrylamide). At lower critical solution temperatures, poly(N-isopropylacrylamide) precipitates out of the solution because it is a hydrophobic polymer at LCST but a water-soluble polymer at lower LCST. Gel that is sensitive to positive temperature has an upper critical solution temperature (UCST) and contracts when it cools down below this point. The swelling of polymer networks containing polyacrylamide and poly-acrylic acid is temperature dependent.

Thermally reversible gels made of poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) are the most widely used kind (Pluronics®, Tetronics®, poloxamer).

pH triggered In situ gelling system

pH is an additional physiological trigger that causes In situ gel formation. This family of polymers includes groups that are basic or acidic and that, in response to varying ambient pH levels, either release or receive protons. These are known as pH-sensitive polymers as a result. The formulation exists as a normal solution at pH 4.4, but gels at pH 7.4. Anionic group-containing pH-sensitive polymers, such as Carbopol® and Carbomer, are primarily derived from polyacrylic acid. Conversely, polyvinyl acetal diethylamino acetate solutions, which have a low viscosity at pH 4, gel in neutral pH conditions. Other polymers that exhibit pH-induced gelation include polyethylene glycol (PEG), polymethacrilic acid (PMMA), and cellulose acetate phthalate (CAP).

b) Ion-activated system

A variance in ionic strength causes the solution to gel. The osmotic gradient that runs across the gel's surface is thought to control how quickly gelation occurs. Hyaluronic acid, alginates, gelrite or gellan gum, and other polymers can all display osmotically driven gelation.

c) In situ gel formation due to physical mechanism

Diffusion

A physical technique called diffusion is employed in the creation of In situ gels. The polymer matrix solidifies or precipitates as a result of the solvent from the polymer solution diffusing into the surrounding tissue in this technique. When creating an In situ gelling system, N-methyl pyrrolidone (NMP) is a polymer that is often utilised.

Swelling

In situ gel can occurs when a substance collects water from its surroundings and expands to fill a desired region. Glycerol mono-oleate, or myverol 18-99, is one such material. It is a polar lipid that expands in water to produce lyotropic liquid crystalline phase structures. It is bioadhesive in some ways and is enzymatically degradable in vivo.

d) In situ gel formation due to Chemical reaction

Enzymatic cross-linking

Enzymatic cross-linking is the best method for creating the In situ gelling system. Using this technique, the gel is created by cross-linking with bodily fluid-containing enzymes. Although the natural enzyme that causes the In situ creation is not as well-studied as it is, it seems to have certain advantages over convective and synthetic methods. For instance, the enzymatic process ensures potency in a physiological condition and eliminates the need for potentially harmful chemicals like initiators or monomers in the dosage. Hydrogels may be used by the intelligent stimuliresponsive delivery system to release insulin. It is also possible to inject the combination prior to gelation by adjusting the amount of enzyme in order to preserve the appropriate mechanism for regulating the pace of gelation.

Ionic crosslinking

The ion-sensitive polymer is employed in this technique. When different ions such as Na+, K^+, Ca^{+2}, and Mg^{+2} are present, ion-sensitive polymers may experience a phase change. Additionally, certain polysaccharides belong to the group of ion-sensitive polymers. Whereas i-carrageenam creates elastic gels primarily in the presence of Ca^{+2}, k^+ carrageenan forms stiff gels that respond to tiny amounts of K^+. Gelrite is the primary brand of gellan gum. It's an anionic polymer that goes through an In situ gelling mechanism when it comes into contact with mono and divalent cations.

Photo-polymerisation

Electromagnetic radiation is utilised in the photopolymerization process to achieve the In situ gelling. Electromagnetic radiation is commonly used in conjunction with a reactive solution macromer to create a gel, as well as a monomer and invaders delivered into the tissue. The ideal polymer is Polymerizable functional groups dissociate when one of these compounds, acrylate, is present. Longwave UV and visible wavelengths are typically used for photoinitiation and monomers, such as macromers. Is UV light with a high frequency rarely utilised? In this procedure, a ketone, such 2,2-dimethoxy-2-phenyl acetophenone, acts as an initiator

for UV photopolymerization, although it is medically hazardous and has restricted tissue penetration. Common visible light systems employ ethyl eosin initiators and camphorquninone.

1.3.4 Evaluation and Characterization of In situ gel [37,38]

a) Clarity:

Visual assessment in excellent lighting with a black and white backdrop was used to assess the clarity of the image.

b) Texture analysis

Texture analysis of gel was measured by use of two fingers that check gel's consistency, firmness and cohesiveness.

c) Gelation point

It is the temperature at which gel transforms from liquid. For thermoreversible vaginal gel, a gelation temperature range of 30-36°C would be appropriate. When test tubes are tilted to a 90° angle, the temperature progressively rises to the "gelation point," which is the point at which formulations no longer flow. When a pH or ion-dependent polymer comes into contact with vaginal fluid, it changes from a sol to a gel.

d) pH

10 ml volumetric flask was filled with one millilitre of the produced gels, and the solution was thinned with distilled water. A digital pH meter that had been previously calibrated using phosphate buffers at pH 4 and pH 7 was used to measure the pH of the resultant solution.

e) Gel strength

A rheometer is used to assess this parameter. A certain amount of gel is made in a beaker from the sol form, depending on the gelling agent's method of action. The beaker containing the gel is elevated at a set rate, allowing the gel to be probed slowly. The probe's variations in load are determined by measuring the probe's immersion depth below the gel's surface.

f) Rheological studies

The Brookfield Viscometer was used to examine the rheological characteristics of In situ gel compositions. At first, the temperature was kept above 40 °C. By increasing the spindle rotational speed from 0.3 to 100 rpm, the rheological parameters were examined and the viscosity (h), shear rate (g), and shear stress (t) were noted. Each measurement was carried out three times.

g) Mucoadhesive force

The goat's nasal cavity was used to cut a piece of nasal mucosa, which was then quickly secured with a rubber band mucosal side out onto each glass vial. The nasal mucosa vials would be kept for five minutes at 37 °C. A second vial containing a portion of the mucosa was attached to the balance inverted, and the first vial was set on a pan with a height adjustment. Each formulation's sample was applied in a predetermined quantity to the first vial's nasal mucosa. In order to bring the mucosal surfaces of the two vials into close contact, the height of the second vial was then changed. Tissues and the sample were allowed to come into close contact for two minutes. After that, the pan's weight would continue to rise until the vials came loose.

h) Drug Content:

A UV/visible spectrophotometer will be used to measure the absorbance of the gel following the appropriate dilution and weighting of the gel in the medium. The absorbance of a standard solution produced in distilled water with a known concentration of the drug will be measured in order to determine the quantity of drug contained in the formulation.

i) In Vitro Diffusion Cell:

The Franz diffusion cell was filled with goat nasal mucosal tissue. The acceptor chamber was filled with a pH 6.4 phosphate buffer. The donor chamber was filled with 1 millilitre of gel. After every five hours of sampling, 2.5 ml of the sample was taken out of the acceptor compartment at a predefined time point and replaced with phosphate buffer pH 6.4.

Conclusion

Nasal drug delivery is a novel platform and it is alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment. Development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetes, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Used of biodegradable, water soluble, thermo sensitive, pH sensitive polymer for the nasal in situ gel formulations can make them more acceptable and excellent drug delivery system. Exploitation of polymeric in situ gels for controlled release of various drugs, good stability and biocompatibility, bioavailability of drug characteristics make the nasal in situ gel dosage forms very reliable. Nasal in situ gel enhanced the nasal residence time due to its viscosity and mucoadhesive strength.

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