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# Review On In-Situ Gel For Nasal Drug Delivery

**Sadhana R. Shahi[1*], Vijaya Dhum[2] Pooja watane[2], Priyanka S. Kale[2]**
*1.Associate Professor, Government College of Pharmacy, Aurangabad, Maharashtra, 431005*
*2. Students, Government College of Pharmacy, Aurangabad, Maharashtra, 431005*

ABSTRACT

The oral route is a strategy that has been in use for many years. Although it is the most popular and widely used method for giving drugs to people orally, various restrictions, such as drug absorption or drug targeting to a specific [1]organ, might make it difficult to administer... To address these issues as well as to advance medication development security and effectiveness In-situ Nasal Delivery is a unique method for medication delivery system for delivering drugs. The medication used in nasal gels is given as a low viscosity solution. The nasal mucosa when in contact with the polymer's conformation transforms to a gel-like state. It is appropriate to use the nasal gel formulation for medications whose oral administration is challenging. Various biodegradable polymers that are used for the formulation of in situ gels include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly(DLlactic acid), poly(DL-lactide-co-glycolide) and poly-caprolactone.

**Keywords:** In situ gel, bioavailability , polymers, nasal drug delivery.

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# INTRODUCTION

For thousands of years, intranasal administration has been used. Nasal therapy is a recognized form of therapy in Indian medicine's "NASAYA" or Ayurvedic system is used[1]. The most ideal route for medicine administration is oral drug delivery. Oral bioavailability of various substances has been shown to be a factor when systemic effects are anticipated. Encouraged the pursuit of more efficient routes for the delivery using a mechanism[2].To increase the speed and level of drug assimilation the main pathway of the nasal mucosa medication distribution using the transmucosal pathway[3]. Parenteral, transdermal, and transmucosal drug administration methods all have different advantages than peroral methods, including the mucosal linings of the nasal, rectal, vaginal, and buccal cavities. administration. This included the potential bypass of the first-pass effect and the avoidance of the need for a tiny dose of a certain medicine. Lowering the dose will lessen the negative effects and, ultimately, lower the expense of treatment. A practical option for the local and systemic distribution of different medicinal substances is intranasal medication. There is a lot of surface area in the nasal mucosa. That allows for a rapid onset of effects and the possibility of direct Delivery to the brain is delayed in order to prevent pass metabolic testing and exhibit non-intrusiveness; may increase patient comfort, convenience, and conformity. The in-situ gel drug administration methods include oral, ophthalmic, vaginal, rectal, intravenous, intraperitoneal, and others. Vaccines can be also administered Gelation using nose as potential route, such as influenza[4]. occurs as a result of crosslinking. Covalent bonding, which can be achieved within the polymer chain chemically cross-linked bonds (bond formation) or non-covalent binding creation.

**Gel**

The transitional condition between the solid and liquid phases is called a gel. The liquid phase is immobilized by the solid component, which is made up of a three-dimensional network of interconnected molecules[5].

**In situ gel**

After the formulation has been applied at the site, a process known as in situ gelation causes a gel to form there. In situ gel phenomenon develops from a liquid drug formulation solution and is transformed into a semi-solid mucoadhesive key depot. The conversion into gel by the influence of stimuli including temperature, pH, and ionic concentration, is possible with substances like Carbopol, cellulose derivatives, lecithin, chitosan, etc.[6]

**Principle of gelling**

The main idea behind in-situ gelling for nasal formulation is that it should be used in nasal fluid. In this procedure, the medication solution is transformed into gel in the nasal cavity after injection.

**Advantage**

1. Easy to administer
2. Excellent bioavailability
3. Increased patient comfort and cooperation.
4. Ample surface area for absorbing drugs
5. Quick reaction
6. Less negative consequences
7. When oral administration of the medication is not appropriate, the nasal route is employed.
8. Transcends the blood–brain barrier
9. One should avoid first pass metabolism.[7]
10. There is no hepatic first-pass metabolism.
11. Quick absorption of drugs.
12. Rapid start of action.
13. Using an absorption enhancer or another method can increase the bioavailability of bigger medication molecules.
14. Greater bioavailability of tiny medication molecules through the nose.

**Disadvantages**

1. These systems are designed as solutions, which are more prone to instability such as chemical deterioration (oxidation, microbial deterioration or hydrolysis, for example.
2. The mixture needs to be stored correctly because if the medication is not properly maintained, it may stability issues.
3. Radiation exposure of particular polymers (e.g., electromagnetic, ultraviolet, and so forth). so causes the development of gel inside the packaging.[8]
4. Requires a lot of fluid.
5. The drug's solar form makes it more biodegradable.
6. Potential stability difficulties resulting from chemical deterioration
7. For a few hours after using the medication, eating and drinking should be limited.
8. Hydrogels can be used to minimize the volume and uniformity of the drug load, especially for hydrophobic medicine
9. Only pills with a tiny dose can be administered increased fluid intake is necessary[9].

10. Chances of stability problems due to chemical degradation.
11. After placing the drug eating and drinking may become restricted up to the few hours.
12. The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drug
13. Only drugs with small dose requirement can be given
14. Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site.[10]

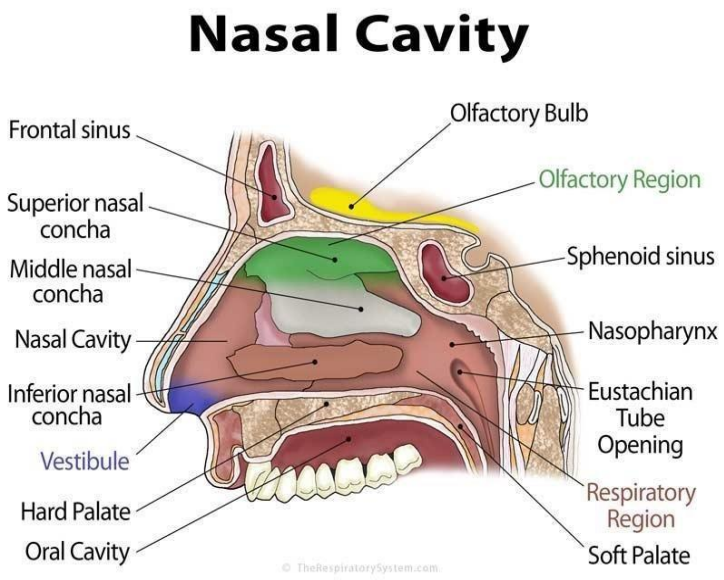
**Ideal Candidate for Drug**

1. The drug shouldn't have any side effects or inflammation of the nose.
2. The recommended drug dose is less than 25mg.
3. It's not advised to use toxic nasal metabolites. within a medication.
4. There shouldn't be any unpleasant odours in drug.
5. Sufficient nasal absorption capacity.
6. Sufficient stability traits.
7. It's not advised to use toxic nasal metabolites medicament contains this.
8. Proper nasal absorption capability[11].
9. The polymer must be attached to the mucosal membrane.
10. It should be risk-free and suitable.
11. .Pseudoplasticity is required.
12. By accelerating cutting, the polymer can reduce viscosity
13. Good tolerance and optical clarity are more ideal for the manufacture of in situ

**Anatomy & physiology of nasal cavity**

The nose is a key organ that filters airborne pollutants and acts as an immune system. The olfactory nerves are in contact with the inspired air and provide the sense of smell, which is closely related to taste perception[12]. The entire volume and surface area of the human nasal cavity are 15–20 ml and 150 cm, respectively. The septum divides the nose into two nasal chambers. Each cavity has a surface area of around 75 cm and a volume of roughly 7.5 ml. Children's mucosal secretions have a pH between 5.0 and 6.7, while adults' secretions have a pH between 5.5 and 6.5. The mucus layer covering the nasal channel epithelium is replaced every 10 to 15 minutes. Every 20 minutes, the nose clears out its interior of particles as the mucus flows through it at a pace of about 5 to 6 mm/min. The goblet cells are found in the mucus membrane that covers the nasal turbinate and atrium. These cells secrete mucus as granules, which thicken in the nasal fluid and add to the mucus layer[13]. Motile cilia cover the cilia cells, and they are

responsible for mucus transport, resulting in mucociliary drug clearance especially in the highly ciliated middle and posterior regions[14].




Each portion can be divided into three regions[15].

**Nasal respiratory region:**

The nasal respiratory region, also known as the conchae, is the largest portion of the nasal cavity. The most crucial area for systemic medication is the respiratory system. delivery.10-12 Components of the respiratory epithelium include There are four different cell types: columnar and non-columnar ciliated cells, goblet cells, and basal cells. the area of the lungs comprises superior, middle, and inferior nasal turbinates. inferior that protrudes from each of the lateral walls of the nasal passage. Nasal and respiratory delivery of systemic medications the mucosa is thought to be the most crucial component.

**Vestibular region:**

The nasal vestibule, which occupies the most anterior part of the nasal cavity and is located just inside the nostrils, measures about 0.6 cm in diameter. This nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands, which is in charge of removing airborne particles. In relation to drug absorption, it is thought to be less significant in the three areas.

**Olfactory region:**

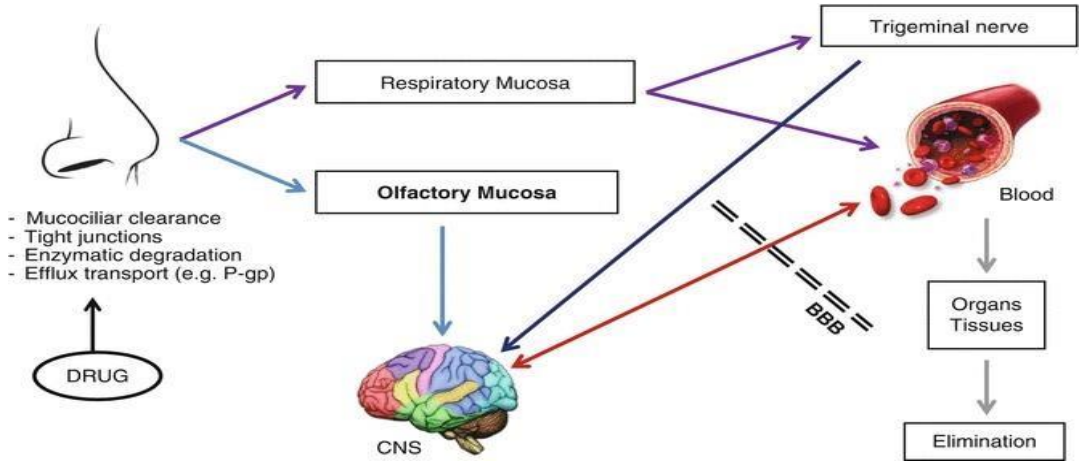
The olfactory region, which is about 10 cm2 in surface area and is situated in the roof of the nasal cavity and extends briefly down the septum and lateral wall, is essential for the transportation of medications to the brain and CSF. The medication can enter the brain through three separate pathways when delivered nasally. The first is the systemic path, via which the drug enters the bloodstream and travels through it to the brain, crossing the blood-brain barrier.

The medication is also carried directly from the nasal cavity to the central nervous system (CNS) via the trigeminal neuronal route and the olfactory area, respectively. In the first pathway, the medication is delivered directly to the primary olfactory epithelial neurons and then transported by intracellular axonal transport to the olfactory bulb, where it may then be distributed to additional brain areas. The second process relies on drug penetration via the olfactory sustentacular epithelial cells via paracellular or transcellular pathways, followed by absorption into the central nervous system (CNS). The final one uses olfactory neurons to engage in pinocytosis.

**Mechanism of Nasal absorption**

The passing through of mucus is the initial step in the drug's absorption from the nasal cavity. This layer is easily penetrated by tiny, neutral particles. It might be more challenging for massive or charged particles to cross, though. The primary mucus protein, mucin, has the capacity to adhere to solutes and obstruct diffusion. Environmental modifications could also cause structural changes in the mucus layer (i.e., pH, temperature, etc.) There are various methods for absorption across the mucosa after a medication has passed through the mucus. These include transcellular or straightforward membrane diffusion, paracellular transport including cell-to-cell migration, and transcytosis by vesicle carriers. Potential metabolism that could occur before the drug reaches the systemic circulation and the drug's short stay in the cavity are barriers to drug absorption. Numerous mechanisms have been suggested, however the two ones listed below[16].

1. The aqueous route of transport, also known as the paracellular route, is part of the first mechanism. The relationship between intranasal absorption and the molecular weight of water-soluble substances is inverse log, and it is a sluggish and passive route. For medicines with a molecular weight more than 1000 Daltons, poor bioavailability was noted.[13]
2. The second mechanism is the transcellular process, which transports drugs that are lipophilic and exhibit rate dependence on their lipophilicity. It transports drugs via a lipoidal route. Drugs can also pass across membranes actively by way of carrier-mediated mechanisms or transfer through the opening of junctions. To help in drug delivery, a natural biopolymer called chitosan can be used to open tight connections between epithelial cells.




**Process for Formulation**

**Cold Approach:**

The medication is mixed with enough cold water in this method. stored overnight at 4 °C in a container made of double distilled water refrigerator. After that, the in-situ gelling polymers are included. gradually while stirring. The mixture is kept in a until a clear solution form in the refrigerator, then volume distilled water is used to adjust. This approach is used when as a gelling polymer, poloxamer, chitosan, or carbopol are employed. Taking into account that poloxamer is dispersed in polymeric form is dissolved at a lower temperature and transforms into a due to the solubility of the nasal temperature increase of Poloxamer's polypropylene oxide chain shrinks at a rapid rate. temperature that causes rain or salting-out of a surface polymer. Likewise, chitosan.

**Hot Method:**

This technique is employed when pectin or gellan gum is the gelling polymer. Gellan chains dissolve in water at high temperatures, take on a random-coil conformation with high segmental mobility, and continue to exist as a solution at higher temperatures. In the presence of ions such as K+ or Ca2+, a phase shift takes place on a cooling gellan gum solution. Similar to how pectin needs a high temperature for demethoxylation .

**Other methods of preparation:**

- Solution polymerization/cross linking
- Suspension polymerization
- Polymerization by irradiation
- Chemically cross-linked hydrogels
- Physically cross-linked hydrogels

**Remedy Polymerization/Crosslinking**

crosslinking agents are used with ionic or neutral monomers in the solution for reaction of copolymerization. Redox initiator system or UV light is employed to start the polymerization reaction thermally. In solvent acting as a heat link, the polymerization reaction, and decreasing temperature control issues Distilled The unreacted monomers are removed using water. the crosslinking agents and catalysts that create the hydrogels. Using this approach, one can create an excellent several kinds of in-situ gels.

**Suspension polymerization**

The suspension polymerization method is used to create spherical hydrogel micro particles with a size range of 1 m to 1 m method. The monomer solution is present in the non-solvent solution. is mixed to create tiny droplets, and a stabilizer is then added. this remedy to keep the tiny droplets stable. Thermal To start, free radical decomposition is used. polymerization. crosslinking agents, unreacted monomers and initiators are eliminated by cleaning prepared surfaces micro particles. The hydrogel is made using this technique. tiny polyvinyl alcohol particles.

**Irradiation-Induced Polymerization**

Unsaturated compound hydrogels can be created utilizing high energy radiation, such as gamma and electron beams. Irradiating a polymer chain with radicals results in the formation of water-based polymer solution The formation of covalent bonds occurs when the macro particles on the various chains recombine and creates a cross-linked structure as a result. plasticization of radiation can cause macro particles to interact with oxygen Furthermore, inert atmosphere radiation is carried out by utilizing argon and nitrogen gas. Polymer examples Polyvinyl alcohol is used in the crosslinking process by radiation. Polyacrylic acid with polyethylene glycol.[17]

**Hydrogels with chemical crosslinking**

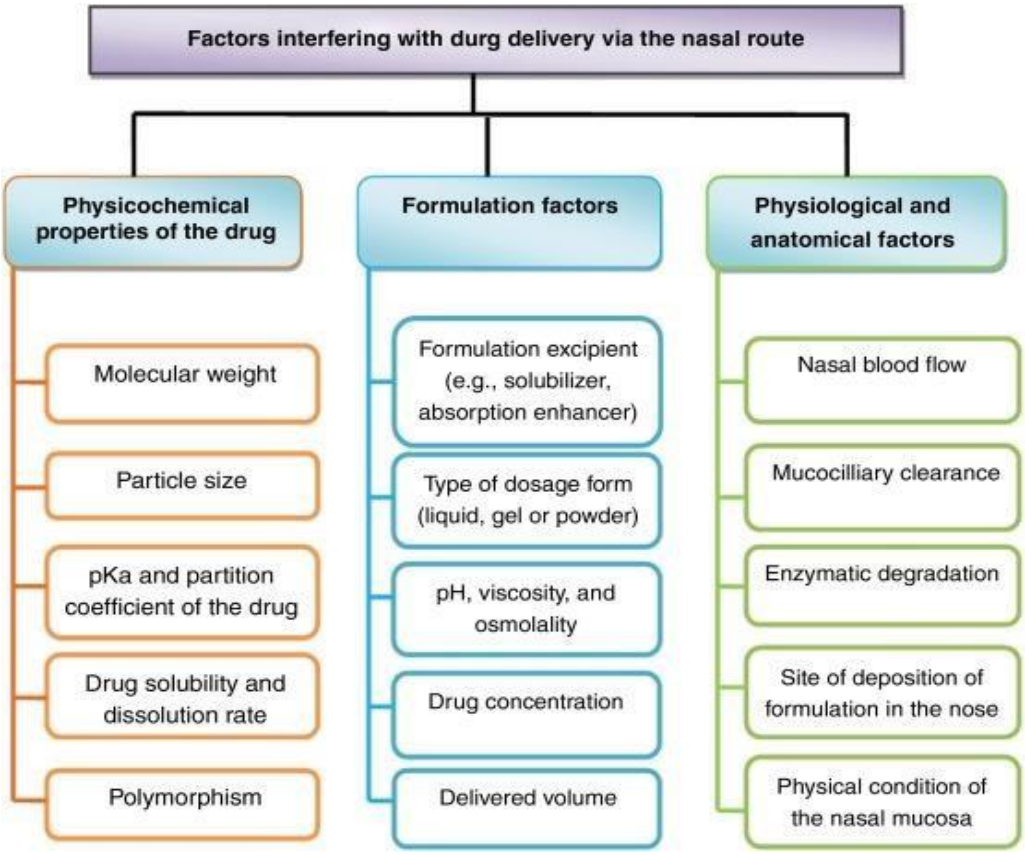
Due to the presence of functional groups, hydrogels can be created by creating a covalent bond between polymer chains and complementary reactivity, such as amine-carboxylic acid. Polymers with functional groups like -OH, -COOH, and -NH2 are soluble in water. Glutaraldehyde is used to crosslink polymers with -OH groups, such as polyvinyl alcohol, to form hydrogels. Reactive functional groups on the polymer react with the crosslinking agent as a result of the addition. Due to their extreme toxicity, unreacted agents must be removed. The reaction is carried out using organic solvents, and water might react with the crosslinking agent. The medicine is placed onto these hydrogels and released as a first-order release after they have formed.

**Hydrogels that are physically cross-linked**

It is well known that the covalent crosslinking agent is hazardous. This issue is solved by using reversible ionic crosslinking to create hydrogels. When chitosan combines with a positively

charged component like ions or molecules, a network of ionic bridges forms between the polymeric chains. It is a quick and painless process. In contrast to covalent crosslinking, auxiliary molecules like catalysts are not necessary. Chitosan polymer can create polyelectrolyte complexes with Polyacrylic acid. [15]

**Factors affecting Nasal Drug Delivery System**




**Polymers used In-Situ Gelling System:**

**Carbopol**

As the pH is increased above its pKa, carbopol exhibits the sol-gel transition. The carboxyl groups of the acidic In water, polymers partially dissociate and start to unravel. create a coil structure that is flexible. In an acidic environment, a little the percentage of carboxyl groups on the polymer create a flexible coil structure by dissociating. in a halogen the carboxyl groups ionize in the environment, producing a negative charge running down the polymer's spine. electric resistance of the anionic group induces the expansion and uncoiling of the molecule that causes polymers to swell and create gels.

**Poloxamer**

Poloxamers are water-soluble tri-block copolymers with an ABA configuration made of two polyethylene oxide and one polypropylene oxide core.

**Properties:**

Commercially available poloxamer, also known as Pluronic, has good thermal setting properties and greater time spent using drugs. It serves as a solubilizing agent and a gelling agent. Poloxamer provides a translucent, colourless gel. Based on the distribution and ratio of hydrophilic and There are many different molecular weights of hydrophobic chains, each with a unique gelling characteristic[18].

**Sodium alginate**

is a salt of alginic acid that is obtained from brown algae. They are polysaccharides in linear blocks. There are two of them monomer types -D-mannuronic acid and -L residues of glucuronic acid connected by 1,4-glycosidic linkages. It is biodegradable and non-toxic. Given its It has good mucoadhesive property due to its carboxylic group. The alginate monomers -D-mannuronic acid and - L-glucuronic acid is organised in an M-M block. changing the (M-G) block sequence. G-block plastic Contacts with molecules of calcium to produce uniform gel formation. mechanical toughness, and the type of hydrogel and the G:M ratio affect the porosity of utilized crosslinker.

**Pectin**

Pectin's are a class of polysaccharides. The primary component of the polymer is - -(1-4)—D Residues of galacturonic acid. Whenever there is free calcium Low methoxy Pectin's (esterification level 50%), ions aqueous solution easily produces gels, which crosslink the chains of galacturonic acid in the manner suggested by egg box model. The gelation of pectin occurs in the presence of H+ ions source of divalent ions, typically calcium, will occur to create the gels that are appropriate for use as vehicles for delivering drugs. Pectin is primarily used for these organic solvents since it is water soluble in formulations. are not incorporated into the formula. there are divalent cations Perform the transformation of pectin to gel in the stomach. Indicate the oral dosage.

**Chitosan**

Using an alkaline process, the polycationic polymer chitosan is biodegradable, thermosensitive, and deacetylation of the shrimp natural substance chitin crab shell, too. The pH of chitosan is biocompatible. reliant, still-dissolved cationic polymer up to a pH of 6.236 in aqueous solutions. Neutralization of aqueous chitosan solution to a pH greater than 6.2 causes the development of a hydrated gel-like substance precipitate. The cationic polysaccharides that gel at this pH changes from a solution to one that is thermally sensitive Aqueous solutions that form a dependent gel without any cross-linking or chemical alteration with the inclusion of single-anionic-head polyol salts, such as salts of glycerol, sorbitol, fructose, or glucose to aqueous chitosan solution.[19]

**Gellan gum**

The tendency of gelation in gellan gum is temperature- or cation-dependent. The in-situ gelling apparatuses included of a gellan solution containing sodium citrate and calcium chloride complexes. The calcium ions were present when it was given orally. Secreted in the stomach's acidic environment, causing the an in-situ gel is created by the gelation of gellan.[20]

**Xanthan Gum**

High molecular weight extracellular polysaccharide called xanthan gum is made by the bacterium Xanthomonas campestris. It is a polysaccharide with a long chain and many side chains of trisaccharide's. Two link the main chain together sugar units. Two side chains make up the side chains. One glucuronic acid unit and one mannose unit. Gum Xanthan can combine with positively charged particles to form a robust gel. polymers. In water, this gum forms a fragile structure. which produces low viscosity high viscosity solutions concentration.

| Polymer | Origin | Charge | Solubility | Mucoadhesive capacity |
|---|---|---|---|---|
| Carbomer | Synthetic | Anionic | Insoluble | +++ |
| Polyacrylic acid | Natural | Anionic | Insoluble | +++ |
| Chitosan | Natural | Cationic | Soluble | ++ |
| Xanthan gum | Natural | Anionic | Insoluble | + |
| Methyl cellulose | Natural | Nonionic | Soluble | + |
| Xyloglucan | Natural | Anionic | Soluble | + |
| Poloxamer | Synthetic | Nonionic | Soluble | ++ |
| Sodium alginate | Natural | Anionic | Soluble | ++ |
| HPMC | Natural | Nonionic | Soluble | + |
| Mucoadhesive capacity : Excellent(+++), Good(++), Poor(+) | | | | |

**Evaluation of in situ gel:**

**Clarity:**

In situ gel's clarity was evaluated visually against a dark background.

**Viscosity:**

Different viscometers, such as the Brookfield viscometer, cone and plate viscometer, may be used to measure the viscosity and rheological characteristics of polymeric compositions in solution or in gel produced with synthetic tissue fluid. These formulations' viscosity ought to be such that patients ought to comply with them.

**Content uniformity:**

All of the manufactured gel formulations underwent a test to determine whether the composition was uniform. The formulation-containing vials (n=3) were thoroughly shaken for two to three minutes. In a 50 ml volumetric flask, 0.1 ml of each formulation was taken, gently dissolved in phosphate buffer solution pH 6.8, and the final volume was adjusted. To achieve a concentration of 2 g/ml, 1 ml of this solution was diluted up to 100 times with phosphate buffer solution, pH 6.8. Using a Bioera Elite UV spectrophotometer and phosphate buffer solution pH 6.8 as a blank, the absorbance was measured at analytical wavelength 276 nm.[21]

**pH of gel**

Using a pH meter that had been previously calibrated using pH 4 and pH 7 standard buffers, the pH of each batch of formulas was tested[22].

**Measurement of gelation temperature and gel melting:**

The temperature at which the liquid phase transforms into a gel can be referred to as the gelation temperature for in situ gel forming systems that use thermo reversible polymers. The liquid mixture is retained in a sample tube, submerged in water, and heated to a set temperature and pace. After that, the samples will be checked for gelation, which is thought to have taken place when the meniscus ceased to move when tilted through 90°C. When the gel begins to flow when tilting past 90°C, the gel melting temperature is a critical temperature that must be noted. When you tilt the tube, the meniscus should not move, which is a sign that gel has formed.

**Gel Strength:**

From the sol form, a predetermined amount of gel is formed in a beaker. The beaker containing the gel is lifted at a specific rate, slowly forcing a rheometer probe through the gel. As a function of the depth of the sample, the variations in the load on the probe can be the probe is submerged beneath the gel's surface.

**High performance liquid chromatography:**

The reversed phase mode of the HPLC system. The entire Nova pack C18 column (150 mm long X 3.9 mm i.e.) is used for analysis.

**Texture analysis:**

Using a texture analyzer, which primarily indicates the syringe ability of the sol so that the formulation may be easily delivered in vivo, the formulation's purity and durability were assessed. Gels need to have higher adhesive qualities in order to maintain tight contact with a tissue-like surface.

**Sterility testing:**

In accordance with IP 1996, sterility testing is done. For this test, incubate the formulation for 14 days in a fluid thioglycollate medium at 30 to 35 °c to look for bacterial growth and in a soybean casein digest medium at 200 to 25 °c to look for fungal growth.

**Appearance:**

The gels should ideally be clear. We looked examined the formulations' overall appearance, including colour, odour, and the presence of dispersed particle matter. Terminal sterilization with autoclaving had no effect on physical, chemical properties of the formulation.

**Homogeneity:**

Watch the particle roughness under the light after sandwiching the preparation between two glasses.

**Drug polymer interaction study & Thermal analysis:**

With the help of Fourier transform infrared (FTIR) spectroscopy, interaction study can be determined. The KBr pellet method can be used to assess the nature of the interacting forces

throughout the gelation process. For in situ forming polymeric systems, thermo gravimetric analysis (TGA) can be used to calculate the amount of water in hydrogel. A differential scanning calorimeter (DSC) was used to compare the thermogram of the mixture to that of the pure active components utilized to produce the gel.

**Accelerated stability studies:**

When aluminum-sealed amber vials fail, the formulation is temporarily changed. According to ICH state regulations, accelerated stability was performed at 40–20 °C and 75–5% RH.

**In vitro Drug release Studies:**

The USP Dissolution Test Apparatus Type II was used to monitor drug release (Zaki et al., 2007). At 35°C +/- 0.5°C and rotation of 50 rpm, a dialysis tube holding 1 ml of gel formulation was submerged in 500 ml of SNEF as a dissolution medium. At intervals of 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes, 1 ml sized aliquots of SNEF were removed and replaced with fresh 1 ml-sized aliquots. As previously noted, spectrophotometric measurements were made on the samples. There were three duplicates of each experiment.[22] In vitro drug release data indicated that prepared nasal gels can maintain the drug in the matrix network and prevent early release of drug their by maintaining their integrity during the study period.[24]

**In vivo drug release:**

One way to measure medication release in the body is to evaluate drug preparation (in vivo). We can create the medicine in accordance with the requirements of pharmacotherapy by understanding the time devastated and the polymer components employed.

**Floating duration:**

The time taken for the formed gel floating on the surface of the dissolution medium is known as floating duration. The duration of the floating of gels was determined by visual inspection in a dissolution test apparatus USP (Type II) containing 500 mL of 0.1N HCl (pH 1.2) at 37±0.5$^0$C.

**Marketed product of In-situ gel:**

**Table 1: Marketed products of Oral floating in situ gels**

| Drug substances | Brand Name | Indication | Dosage form | Manufacturer |
|---|---|---|---|---|
| Levodopa, Benserazide | Modapar | Indicated for the prevention of Parkinson's disease | Floating capsule | Roche Products, USA |
| Diazepam | Valrelease | Indicated to treat management of anxiety disorders | Floating capsule | Hoffmann-LaRoche, USA |
| Aluminium hydroxide, Magnesium carbonate | Liquid Gaviscon | Indicated to treat the symptoms of too much stomach acid such as stomach upset, heartburn and acid indigestion | Effervescent Floating Liquid , Alginate Preparation | Glaxo Smith Kline, INDIA |

**Table 2-Marketed products of ophthalmic in situ gels**

| Drug substances | Brand name | Indication | Dosage form | Manufacturer |
|---|---|---|---|---|
| Timolol maleate | Timoptic-XE | Indicated in the prevention of raised intraocular pressure in patients with open ocular hypertension or angle glaucoma | Solution | Merck and Co. Inc |
| Azithro-mycin | Azasite | Indicated for the prevention of bacteria caused by sensitive conjunctivitis isolated of some microorganism i.e. Haemophilus influenza,Staphylococcus aureus, streptococcus mitis group, streptococcus pneumoniae | Solution | In-Site Vision |
| Lidocaine hydrocloride | Akten TM | Suitable for treating eye surface anesthetics during ophthalmological procedures | Gel | Akten |

**Table 3: Marketed products of Nasal in situ gels**

| Drug substances | Brand name | Indication | Dosage form | Manufacturer |
|---|---|---|---|---|
| Fluconazole | Diflucan | Used to prevent the Antifungal infections | Solution (Spray) | Pfizer Limited, India |
| Zinc gluconate, Zinc acetate | Zicam | Used to prevent cold and the relief of cold symptoms such as sore throat, runny nose, cough and congestion | Solution (Spray) | Matrixx Initiatives, Inc |

**Tables 4: Marketed products of Rectal and Vaginal in situ gels**

| Drug substances | Brand name | Indication | Dosage form | Manufacturer |
|---|---|---|---|---|
| Metronidazole | Metrogel Vaginal | Used to prevent certain types of bacterial infections in the vagina | Gel | JM Pharmaceuticals |
| Progesterone | Crinone | Used to prevent gynecological disorders | Gel | Watson Pharma, Inc. |

**Table 5: Marketed products of injectable in situ gels** Error! Bookmark not defined.

| Drug substances | Brand name | Indication | Dosage form | Manufacturer |
|---|---|---|---|---|
| Ganciclovir | Vitrasert | Used to prevent cytomegalovirus infections | In situ gel | Bausch Health Companies Inc. |
| Doxycycline | Atridox | Used to prevent adult gum disease (periodontitis) | Gel | DenMat |
| Leuprolide acetate | Eligard | Used to prevent breast cancer, endometriosis, prostate cancer, uterine fibroids, and primary puberty | Injectable suspension | Tolmar Pharmaceuticals |

**Application of in situ gel Drug delivery system-**

**Oral Drug delivery systems**

The natural polymers employed for in situ producing oral drug delivery systems are pectin, xyloglucan, and gellan gum. Although the presence of H+ ions, a source of divalent ions, will cause pectin to gel, calcium ions are typically needed to form the gels that are appropriate for use as drug delivery vehicles. There has been research on the possibilities of an oral in situ gelling pectin formulation for paracetamol administration[25.]

**Ocular Drug delivery systems**

For in situ gel best ocular delivery, natural polymer such as gellan gum, Alginic acid, xyloglucana common natural polymer employed in the ocular delivery system. To treat intra ocular intolerance in glaucoma, the local system is employed to deliver several ophthalmic substances like independent medicines, anti-inflammatory agents, and antibacterial agents. In-situ gel was used to solve the issue of ocular bioavailability because the usual delivery route is frequently found to be unavailable and therapeutic response owing to excessive fluid retention and energy leads to the quick removal of the drug in the eye. In order to lengthen the composition's early stay and increase availability, which is simpler to perform, viscosity enhancers such carbomers, poly vinyl alcohol, and hydroxypropyl methyl cellulose are employed to raise the composition's viscosity. Surfactants are utilized to promote corneal medication penetration as a protective, misleading agent.

**Nasal Drug delivery systems**

Xanthan gum and gallan gum are employed as in-situ gel polymers in the nasal in-situ gel system to investigate the efficacy of momethasone furoate in the treatment of allergic rhinitis. The modelling of allergen rhinitis and the impact of in-situ gel on nasal antigen signals in rat consciousness are both done using animal experiments. It has been discovered that in-situ gel, as opposed to nosonex marketing changes (Momethasone furoate solution 0.05%), prevents a rise in nasal symptoms.

**Rectal Drug delivery systems**

Additionally, it has a potential use for in situ gels for rectal and vaginal medication delivery. Indomethacin rectal medication administration using xyloglucan-based thermoreversible gels was studied by Miyazaki et al.

**Vaginal Drug delivery systems**

For the treatment of vaginitis, a mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating clotrimazole - cyclodextrin complex was developed. It improves therapeutic effectiveness and patient compliance. To provide a lengthy residence time at the application site,

Pluronic F-127 was employed as an in-situ gel forming polymer with mucoadhesive polymers such Carbopol 934 and hydroxyl propyl methyl cellulose.

**Injectable Drug delivery systems**

An innovative, injectable, thermosensitive in situ gelling hydrogel was created for the treatment of tumours. It comprises of a chitosan solution containing medications that has been glycerophosphate-neutralized

**Dermal and transdermal drug delivery**

An administration vehicle for indomethacin has been tested using pluronic F127 in heat-releasing gel. A 20% weight-to-weight aqueous gel may be employed as an efficient foundation for medication topical delivery, according to in-vivo studies. Insulin permeation interactions have been developed as a result of the iontophoresis and chemical improvements.

## CONCLUSION

Nasal therapy is a recognized form of therapy in Indian medicine's "NASAYA" or Ayurvedic system. The most ideal route for medicine administration is oral drug delivery. Parenteral, transdermal, and transmucosal drug administration methods all have different advantages. In situ gel phenomenon develops from a liquid drug formulation solution and is transformed into a semi-solid mucoadhesive key depot. The conversion into gel by the influence of stimulis possible with substances like Carbopol, cellulose, lecithin, chitosan, etc. For a few hours after using the medication, eating and drinking should be limited. Hydrogels can be used to minimize the volume and uniformity of the drug load. Only pills with a tiny dose can be administered increased fluid intake is necessary. Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel. The entire volume and surface area of the human nasal cavity are 15–20 ml and 150 cm. The septum divides the nose into two nasal chambers. There are four different cell types: columnar and non-columnar ciliated cells, goblet cells, and basal cells.

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