

## Review on Formulation and Evaluation of Nasal In-Situ Gel Drug Delivery System

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**ABSTRACT:** Intranasal administration of antihistamines, antibiotics, vasoconstrictors, and decongestants has been used for decades. It is a non-invasive route for drugs, the nasal offers numerous benefits as a target tissue for drug delivery or can be administered intranasally for topical, systemic, and CNS action. It offers better systemic bioavailability, increases the nasal residence time, directs transport into the systemic circulation and CNS, lowers the risk of an overdose of CNS-acting drugs, decreases the frequency of drug administration, and increases permeability. The nasal route is rich in vasculature and is highly permeable because it allows a greater molecular mass of around 1000 Da. In situ, gelling is in a sol state before administration and can form gels in response to different indigenous stimuli. Natural, synthetic, and semi-synthetic polymers within in situ gelling behavior can be used alone or in combination for the preparation of such systems. It provides sustained and prolonged action in comparison to conventional drug delivery systems. In situ, gelling systems can be formed by pH-triggered systems and can be temperature-sensitive and ion-sensitive. This review is focused on nasal anatomy, physiology, histological and biological parameters, advantages and disadvantages, the composition of in situ gel, application and in situ gels' evaluation, and physicochemical and pharmaceutical factors that must be considered during the preformulation and development of nasal drugs.

**KEYWORDS:** -Nasal drug delivery, Nasal in situ gels, sustained drug delivery, pH triggered, ion-sensitive system, thermos sensitive, gelation, polymers, bioavailability, CNS.

### I. INTRODUCTION:

[1]The nasal route of administration gives better systemic bioavailability than the oral route. It can be a route of drugs that cannot be given orally. In-situ gel systems and their development have received considerable attention over the ages. In-

situ gel releases the drug sustainably maintaining the relatively constant plasma profiles respectively.

These are hydrogels that are liquid at room temperature and undergo gelation when in contact with body fluids or a change in pH. They also have characteristic properties as follows:

#### (A) Physiological Stimuli –

- Thermal Dependent
- pH-Dependent
- Cation-Induced Gelation
- Solvent Exchange and Swelling

#### (B) Chemical Reactions -

- UV Radiation
- Ionic Crosslinking
- Ion-Activated System
- 

#### In-situ forms of Drug Delivery Systems Possess Potential Advantages:

- Simple Manufacturing Processes
- Ease Of Administration
- Reduced Frequency of Administration
- Patient Compliance and Comfort
- Biocompatible
- Good Stability
- Uniform Dose.

It is an extended drug delivery system. The aim of varied drug delivery and drug-directing systems is diminishing drug degradation and damage, thus increasing bioavailability and avoiding undesired effects.

Nasal mucosa possesses neutral pH which is considered a potential route of administration for achieving a faster and higher point of drug absorption since its permeability is higher than the digestive tract, as it lacks abdominal as well as pancreatic enzymatic activity. **The nasal route successfully bypasses the blood-brain barrier and delivers the drug to the CNS.**

### II.[2]:

The brain is a complex organ that is protected from the external environment by various

mechanisms. Unfortunately, these same mechanisms make it difficult to deliver therapeutic agents to the central nervous system. The tight junctions of the blood-brain barrier surrounding the brain create a high transendothelial electric resistance that impedes the systemic delivery of CNS-active drugs. Additionally, if drugs pass through the BBB, multidrug efflux protein transporters may reduce brain exposure. The difficulty of bypassing these brain-protective mechanisms has led to the development of strategies for brain drug delivery, with intranasal delivery emerging as a promising approach.

### III.[3]IN-SITU GEL:

Polymer cross-linking of chain results in gelation which can be obtained by covalent bond accumulation (chemical crosslinking) or non-covalent bond accumulation (physical crosslinking).

In situ, the gel is executed for targeted delivery through vaginal mucosa, rectal routes, and nasal mucosa avoiding the hepatic first-pass metabolism, which is essential for the delivery of proteins and peptides that are as such administered via the i.v. Route because of their sensitivity to GI protease. Hence, it can be used for acute and chronic, disorders or diseases via the intranasal route.

**There are various routes for in situ gel drug delivery, for, example, nasal, oral, ocular, vaginal, rectal, injectable, dermal, transdermal, etc.**

### IV.[4] APPLICATIONS OF IN-SITU GELLING SYSTEM:

#### Oral in situ gelling systems:

In this article, the use of pH-sensitive hydrogels to deliver drugs to specific areas of the gastrointestinal tract is discussed. Various types of hydrogels, including those made from silicone microspheres and dextran, have been developed for site-specific drug delivery. Natural polymers such as xyloglucan, pectin, and gellan gum have been used in oral in situ gel distribution processes. A formulation using pectin was established for the continuous distribution of pcm, without the need for an organic solvent due to pectin's water solubility.

#### In Situ Gels as Ophthalmic Drug Delivery Systems:

Natural polymers are normally used in the optical delivery system, like gellan gum, alginic

acid, and xyloglucan. To relieve intraocular glaucoma stress in the local ophthalmic delivery system several combinations such as an anti-inflammatory agent, an antimicrobial agent, and autonomic medications are used. Because of the high development and dynamics of tear fluid, it has been designed to answer the ophthalmic in-situ gel bioavailability problem. The traditional delivery system also leads to low availability and remedial response, allowing the drug to be extracted fluently from the eye. Viscosity enhancers like Poly Vinyl alcohol, Carbomers, Carboxy Methyl Cellulose, and Hydroxy Propyl Methyl Cellulose are used in optical preparations to enhance the viscous nature of these formulations, thereby accelerating the precorneal residence time and increasing bioavailability. To increase the infiltration of corneal ingredients like surfactants, preservers, and chelating agents' penetration enhancers are used.

#### Nasal Drug Delivery:

The use of gum gellan and gum xanthan polymers in in-situ nasal formation for the treatment of allergic rhinitis with Mometasone furoate was evaluated using sensitized rats as a model for in vivo experiments. In comparison to the marketed nosonex preparation, the in-situ gel showed resistance to antigen-induced nasal symptoms.

#### Rectal System of Drug Delivery:

This method is effective for prescribing various types of medications, such as liquids, semi-solids (liniments, emulsions, and froths), and suppositories in solid form. Classic suppositories may cause discomfort during insertion and cannot be held at a single rectal site, potentially leading to drug inefficiency. Choi et al developed temperature-sensitive liquid suppositories that gel at 30-36°C for rectal and vaginal drug delivery, while Miyazaki et al formulated an in-situ gel of Indomethacin for rectal delivery using a thermo-reversible xyloglucan-based gel, which showed improved medication absorption and prolonged drug residence time in rabbits compared to commercial suppositories.

#### Vaginal In Situ Gels:

Vaginal drug delivery using a thermoplastic graft copolymer undergoing in situ gelation has been shown to provide continuous release of active ingredients like estrogens,

peptides, progestins, and proteins. A recent report suggests that mucoadhesive thermosensitive gels combining poloxamers and polycarbophil increase and maintain the antifungal effectiveness of clotrimazole drug compared to polyethylene glycol-based formulations.

#### Injectable in Situ Gels:

Injectable or implantable delivery systems like poloxamer gels have been researched for extended-release medications. These gels, with or without viscosity enhancers, have been tested for epidural administration of drugs, intramuscular and subcutaneous administration of human growth hormone, and creating prolonged-acting single-dose lidocaine injectable. They have also been used to create novel types of depot protein injectable managed-release formulations. An in-situ forming gel has been employed to minimize postoperative peritoneal adhesion.

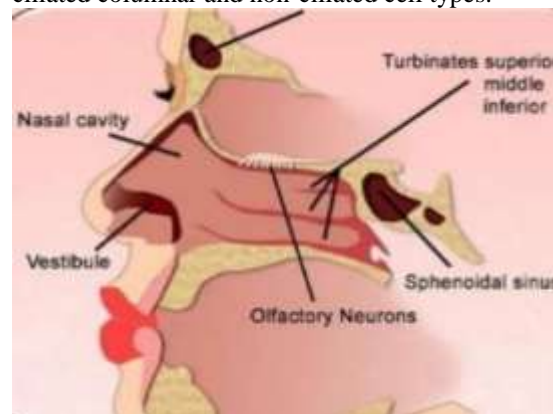
#### In Situ Gels as Dermal and Transdermal Drug Delivery Systems:

Percutaneous administration of indomethacin used a thermally reversible Pluronic gel as a vehicle. Studies in animals show that a 20% aqueous gel is useful for topical drug administration. Transdermal insulin delivery was achieved with poloxamer 407 gels and enhanced by iontophoresis and chemical enhancers.

#### V.[2,5]ANATOMY AND PHYSIOLOGY OF NASAL CAVITY:

The nasal cavity is the uppermost part of the respiratory tract which consists of the olfactory senses. The nose is divided into two nasal cavities with the septum called mesethmoid. The nasal cavities' epithelium is lined by a mucus layer which is regenerated every 10-15 mins. The volume of the nasal cavity is approximately 15ml with a surface area of 150 cm<sup>2</sup>. For systemic drug delivery, the

respiratory region has high significance. The epithelial lining of this region comprises basal cells, goblet cells having mucus in them, and ciliated columnar and non-ciliated cell types.

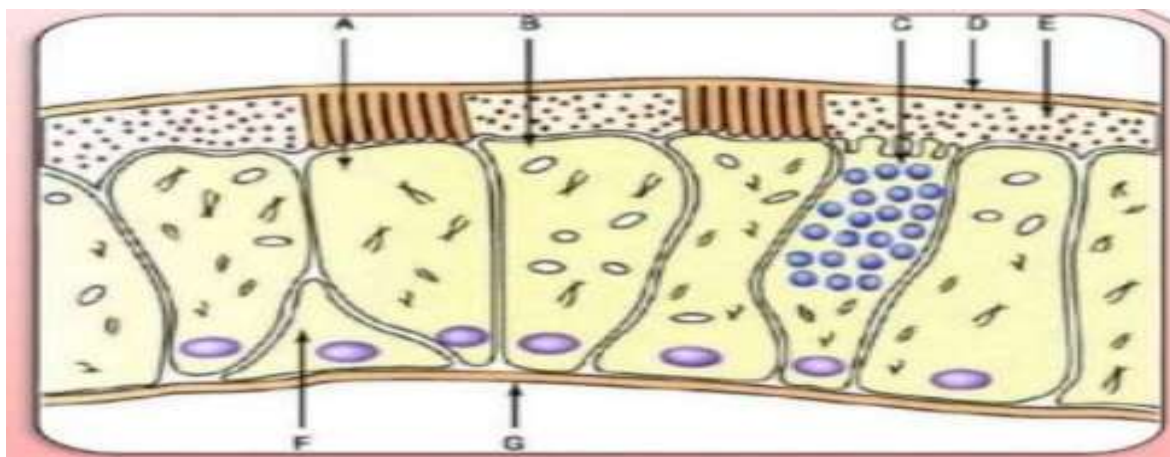


**FIG.1: PARTS OF THE NASAL CAVITY CONSIST OF THE NASAL VESTIBULE, INFERIOR TURBINATE, MIDDLE TURBINATE, SUPERIOR TURBINATE, AND OLFACTORY NEURONS**

The cilia in the lining move in the form of waves to transport the particles in the pharynx area for ingestion. It covers about 300 microvilli that provide a large surface area for absorption beneath the epithelium – lamia propria, blood vessels, nerves, serous glands, and mucus secretory glands can be found.

The pH range of mucosal secretions is from 5.5 to 6.5 in adults and 5 to 6.7 in children. The mucus moves across the nose at an approximate rate of 5 to 6 mm per minute leading to particle clearance within the nose every 20 min.

The nasal cavity accounts for numerous enzymes. In humans, CYP450 AND its forms are being identified. Other enzymes include carboxyl esterases and glutathione-S transferases.



**FIG.2:** CELL TYPE OF THE NASAL EPITHELIUM SHOWING CILIATED CELL (A) NON-CILIATED CELL (B) GOBLET CELLS (C) GEL MUCUS LAYER (D) SOL LAYER (E) BASAL CELL (F) BASEMENT MEMBRANE

The 2 symmetrical halves, one opening at the face through the nostrils and extending posteriorly to the nasal pharynx. The halves consist of 4 areas: nasal

**NASAL VESTIBULE:**

It is the anterior portion of the nasal cavity that is just inside the nostrils and presents an area of about 0.6cm<sup>2</sup>. The nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands. The nasal vestibule characteristics are desirable to afford, and high resistance against environmental factors but at the same time absorption of substances including drugs is difficult in this region.

**ATRIUM :**

An intermediate media between the vestibule and respiratory region. Its anterior portion is constituted by stratified squamous epithelium whereas the posterior area is by pseudostratified columnar cells present in microvilli.

**RESPIRATORY REGION :**

The nasal respiratory region is the most significant part of the nasal cavity known as the conchae subdivided into superior, middle, and inferior turbinates. These specialized structures regulate humidification, and temperature regulation of the air inhaled. The respiratory mucosa is an essential section for delivering drugs systemically. The nasal epithelium is covered with a thin mucus

vestibule, atrium, respiratory region, and olfactory region, which are further classified according to their anatomy and histological characteristics.

layer – produced by goblet cells and secretory glands which further secrete granules filled with mucin a glycoprotein that provides viscosity to the mucus.

**OLFACTORY REGION :**

The olfactory region is present in the roof of the nasal cavity. Its neuro epithelium is the only part of the CNS exposed to the external environment directly. The area contains small serous glands (Bowman's glands) that secrete a solvent for odoriferous substances.

**VI.[3]MECHANISM OF NASAL ABSORPTION:**

1. First mechanism: The aqueous route of transport, also known as the paracellular route, is slow and passive. Intranasal absorption and water-soluble compound molecular weight have an inverse log-log correlation. Compounds with a molecular weight greater than 1000 Daltons have poor bioavailability.
2. Second mechanism: Transporting lipophilic drugs through cell membranes can occur via a lipoidal route, also known as the transcellular process. Active transport via carrier-mediated means or through the opening is also possible.

**VII.[1] TYPES OF NASAL FORMULATIONS-**



**FIG 3: TYPES OF NASAL FORMULATION**

**VIII.[1,5,6,7]ADVANTAGES AND DISADVANTAGES OF NASAL DRUG ABSORPTION-**

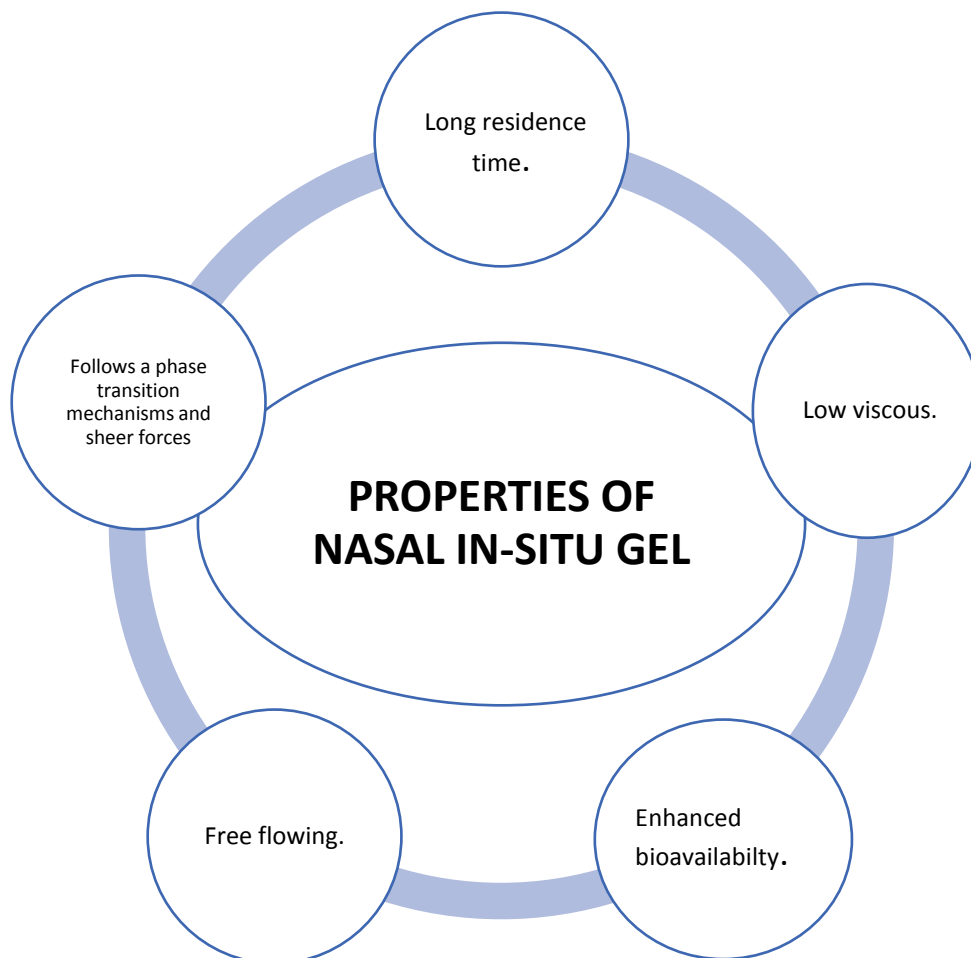
ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none"> <li>•Increased residence time of the drug in the nasal cavity.</li> </ul>	<ul style="list-style-type: none"> <li>•Not well-known drug transport mechanism</li> </ul>
<ul style="list-style-type: none"> <li>• Decreased frequency of drug administration.</li> </ul>	<ul style="list-style-type: none"> <li>•Surface area is less as compared to GIT</li> </ul>
<ul style="list-style-type: none"> <li>• Results in rapid absorption and onset of effect.</li> </ul>	<ul style="list-style-type: none"> <li>•Limited volume can be sprayed</li> </ul>
<ul style="list-style-type: none"> <li>•Avoids degradation of the drug in the gastrointestinal tract resulting from acidic or enzymatic degradation.</li> </ul>	<ul style="list-style-type: none"> <li>•Suitable for potent drug</li> </ul>
<ul style="list-style-type: none"> <li>•Low dose required.</li> </ul>	<ul style="list-style-type: none"> <li>• Loss of dosage due to mechanical technical aspects</li> </ul>
<ul style="list-style-type: none"> <li>• Minimized local and systemic side effects.</li> </ul>	<ul style="list-style-type: none"> <li>• Mucosal damage</li> </ul>
<ul style="list-style-type: none"> <li>•Improved bioavailability of the drug</li> </ul>	<ul style="list-style-type: none"> <li>• Nasal mucosal irritation</li> </ul>
<ul style="list-style-type: none"> <li>• Direct transport into the systemic circulation and CNS, is possible</li> </ul>	<ul style="list-style-type: none"> <li>•Irreversible damage of the cilia on the nasal mucosa.</li> </ul>
<ul style="list-style-type: none"> <li>• Offers lower risk of an overdose of CNS-acting drug</li> </ul>	
<ul style="list-style-type: none"> <li>• Improved patient compliance.</li> </ul>	

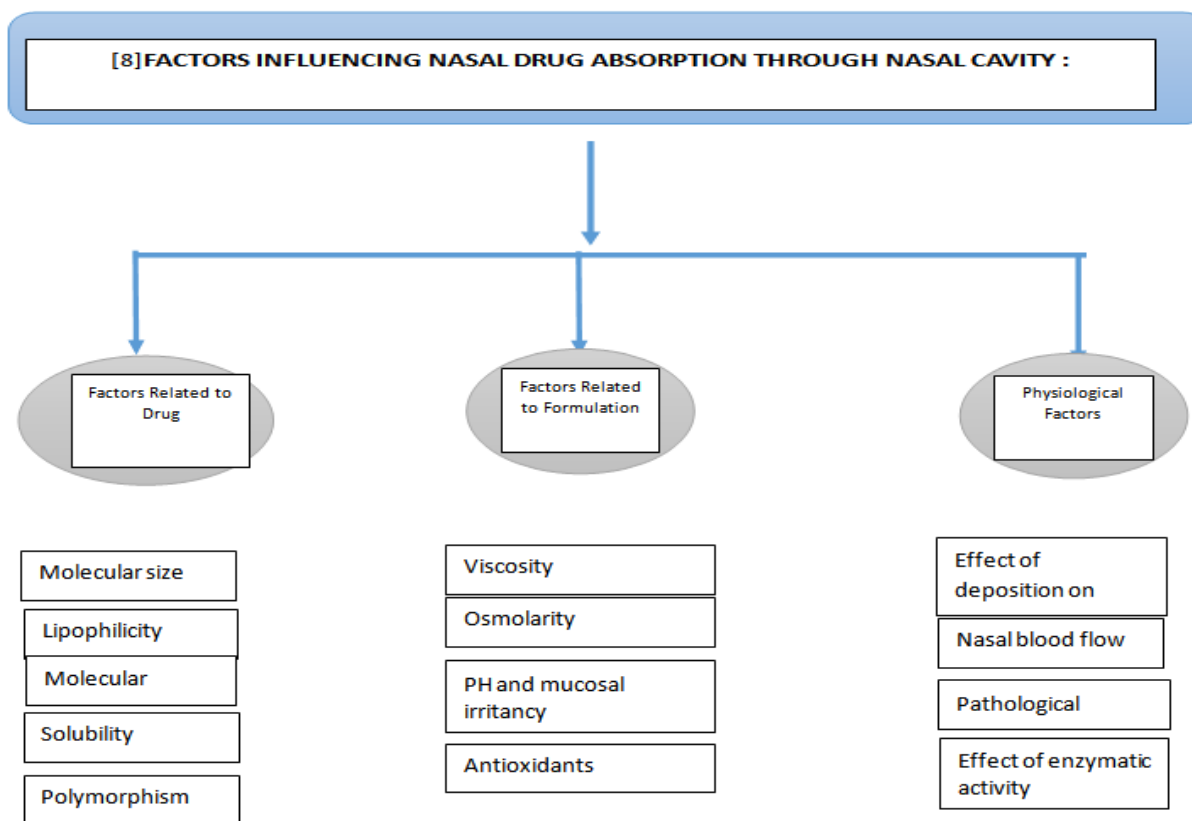
### IX.[6]IN – SITU GELS

In-situ, gelation is a process of gel formation at the site of action after the formulation has been applied at that site. It is the phenomenon based upon a liquid solution of drug formulation and converted into a semi-solid muco adhesive key depot.

### X.[6]PRINCIPLE OF GELLING

The main principle of gelling for the nasal formulation is to apply it in nasal fluid and after administration, the drug solution is converted into a gel in the nasal cavity.





#### XI. TYPES OF IN-SITU GEL:

- Thermo- sensitive in situ- gels
- pH-sensitive in situ gels
- Ion-sensitive in situ gels

#### [1,9,10] APPROACHES OF IN-SITU GELLING SYSTEM:

[1] Various approaches for an in-situ gelling system :

##### A) Stimuli-Responsive In-Situ Gelling System

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

##### B) Osmotically Induced In-Situ Gelling System

##### C) Chemically Induced In-Situ Gelling System

- Ionic cross-linking.
- Enzymatic cross-linking.
- Photopolymerization.

##### D) In situ formation based on the physical mechanism.

#### A) STIMULI-RESPONSIVE IN-SITU GELLING SYSTEM -

##### • [11,12] TEMPERATURE-SENSITIVE IN-SITU GELLING SYSTEM:

Temperature-sensitive in-situ gelling systems are the most researched type of stimuli-sensitive polymer systems. Temperature changes trigger a sol-gel transition in polymer solutions. Hydrogen bonds cause the dissolution of polymer chains below the lower critical solution temperature (LCST), while above LCST; hydrophobic interactions promote sol-gel transformation.

a) [5] **Negatively thermo-sensitive:** Negative temperature-sensitive gel had a lower critical solution temperature (LCST) and contract upon heating above the LCST.

b) [5] **Positively thermo-sensitive:** Positive temperature-sensitive gel had an upper critical solution temperature (UCST).

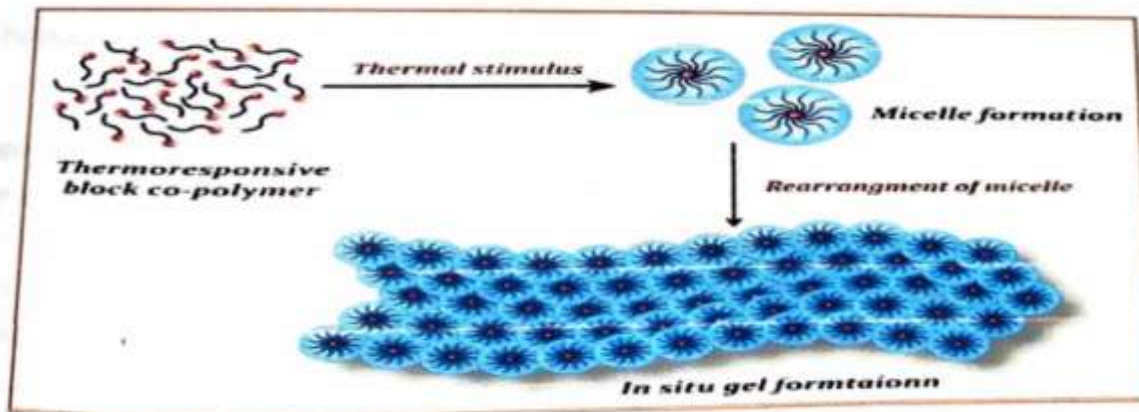


FIG: 4 [11,12] THERMAL IN – SITU GELLING SYSTEM

● [13,14] pH TRIGGERED IN – SITU GELLING SYSTEMS:

All pH-sensitive polymers contain acidic or basic groups that either accept or release protons depending on the environmental pH. Anionic groups cause the gel to swell as external pH

increases, while cationic groups cause it to decrease. PH-responsive polymers are used with drugs and viscosity enhancers at physiological pH. In-situ gelation occurs as the pH changes, forming a polymeric network.

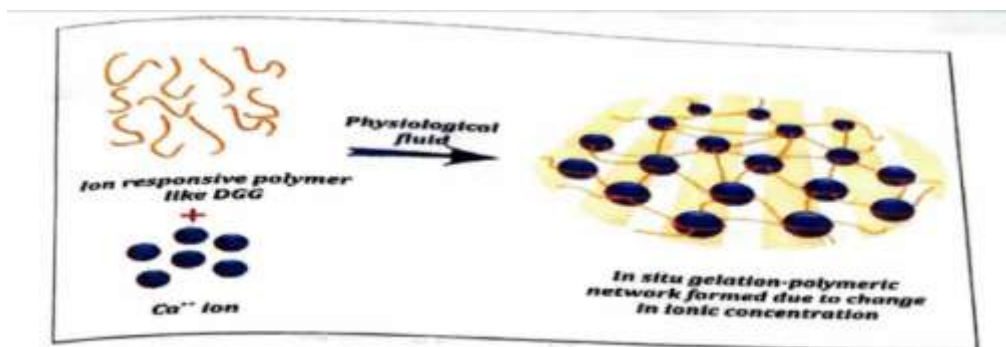


FIG 5:[ 13,14] pH TRIGGERED IN – SITU GELLING SYSTEMS

[1]B) OSMOTICALLY INDUCED IN-SITU GELLING SYSTEM:

In this system, gelling of the solution is triggered by changes in ionic strength. It is considered that the rate of gelation depends on the osmotic gradient across the surface of the gel. The aqueous solution of polymer forms a clear solution which forms a clear gel in the presence of cations like mono or divalent cations. The polymer-like gellan gum and alginates show osmotically induced gelation.

[1]C) CHEMICALLY INDUCED IN-SITU GELLING SYSTEM :

The chemical reaction which forms in-situ gel systems is ionic crosslinking, enzymatic cross-linking, and photopolymerization.

● [15,16] ION-CROSS LINKING IN SITU GELLING SYSTEMS:

In situ, formation is based on chemical reactions, following chemical reactions cause gelation, and undergo in situ gelling in the presence of mono and divalent cations, including Ca<sup>2+</sup>, Mg<sup>2+</sup>, K<sup>+</sup>, and Na<sup>+</sup>. Alginic acid undergoes gelation in the presence of divalent/polyvalent cations.



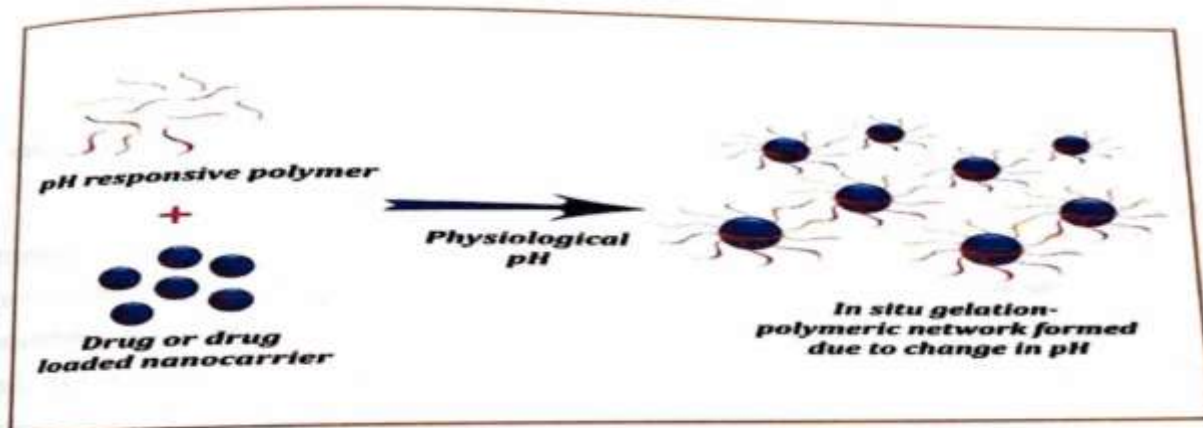


FIG 6: [15,16] ION-CROSS LINKING IN SITU GELLING SYSTEMS

- **ENZYMATIC CROSS-LINKING:** In-situ formation catalyzed by natural enzymes has not been investigated widely but this system has some advantages over other approaches. For example, an enzymatic process performs effectively under physiologic conditions without the need for potentially harmful chemicals like monomers and initiators.
- **PHOTO POLYMERIZATION:** This system when introduced to the desired site with injection gets photocured in situ with the help of Fiber optic cables and then the drug is released for a prolonged period from the system. A photopolymerization, biodegradable hydrogels as a tissue contacting material, and controlled release carrier.

[1]D) IN SITU FORMATION BASED ON THE PHYSICAL MECHANISM:

- **SWELLING** – In situ formation can also occur when water is absorbed by the material from the surrounding environment and expands to occur desired space. Substance like myverol 18-99 (glycerol monooleate), contain polar lipid that swells in water to make lyotropic liquid crystalline phase structures. It has some bio-adhesive properties and may be degraded in vivo by enzymatic action.
- **DIFFUSION** -This method involves the diffusion of the solvent into the surrounding tissue from a polymer solution and leads to precipitation or solidification of the polymer matrix. N methyl pyrrolidone (NMP) solvent is beneficial for this type of system.

[1,3,17 ]METHODS OF FORMULATION OF IN-SITU GELLING SYSTEMS:

- **COLD METHOD**
- **HOT METHOD.**

**Cold Method:** In this method, the drug is stirred with double distilled water and kept overnight at 4°C. The gelling polymer is slowly added with continuous stirring. The dispersion is stored in a refrigerator until a clear solution is formed, and the volume is adjusted. This method is used for poloxamer, chitosan, or Carbopol as gelling polymers. Poloxamer and chitosan require low temperatures to remain as a solution.

**Hot Method:** This method is used when gellan gum or pectin is the gelling agent. Gellan chains dissolve in water at high temperatures and remain as a solution. Sol-gel transition occurs on cooling the solution in the presence of ions like K<sup>+</sup> or Ca<sup>2+</sup>. Pectin requires a higher temperature for demethylation, which helps in the formation of the solution.

**DRUG SELECTION CRITERIA :**

- [6]**Molecular Weight and Size:**  
The drug molecules selected for nasal in situ gel should possess an optimal molecular weight and size. A balance needs to be struck between the drug's size and its ability to freely diffuse across the nasal mucosa. Large-sized molecules may face difficulty in penetrating the nasal epithelium, leading to poor drug absorption.
- [6,18]**Solubility:**  
The drug should exhibit good solubility in the gel system to ensure homogeneous drug distribution. Poorly soluble drugs may result in drug precipitation, which can lead to erratic drug release and reduced therapeutic efficacy. Hence,

drug candidates with higher solubility in the in-situ gel matrix should be preferred.

- **[18]Stability:**

Drug candidates for nasal in situ gel should be chemically stable and resistant to degradation. The gel matrix should not cause any interaction or degradation of the drug molecule, as this can render the formulation ineffective. Stability studies should be conducted to determine the drug's compatibility with the gel excipients and its potential for degradation.

- **Pharmacokinetics and Pharmacodynamics:**

A thorough understanding of the drug's pharmacokinetic and pharmacodynamic profile is necessary. Drugs with a short half-life or narrow therapeutic window may not be suitable for nasal in situ gel formulations. The formulation should sustain drug release and maintain therapeutic concentrations for an extended period, while also achieving the desired pharmacological response.

- **Safety and Tolerability:**

The selected drug should possess a high level of safety and tolerability. Nasal administration bypasses the hepatic first-pass metabolism, increasing the drug's bioavailability. This makes it imperative to choose drugs with a low incidence of adverse effects, minimal nasal irritation, and no potential for systemic toxicity.

- **Biocompatibility:**

The drug should be biocompatible with the nasal mucosa, ensuring minimal tissue irritation or damage upon administration. An ideal drug for nasal in situ gel should maintain the integrity of the nasal epithelium and have no cytotoxic effects.

- **Patient Compliance:**

The ease of administration and patient comfort are crucial factors for successful drug delivery. The selected drug should be amenable to the in-situ gel formulation, enabling easy administration via nasal spray devices. A patient-friendly formulation would enhance patient

compliance and thereby improve treatment outcomes.

- **[19]Spreadability:**

In situ, the gel needs to have suitable spreadability to administer easily and to spread easily on nasal mucosa without leakage after administration.

- **[6,7,19]Gel strength:**

The gel strength was found to be affected by concentrations of gelling and bio-adhesive polymers. The nasal gel formulation must have suitable gel strength.

- **Prior Research and Clinical Data:**

It is essential to review the existing literature and clinical data related to the drug candidate. Previous studies and clinical trials can provide valuable insights into the drug's suitability for nasal in situ gel formulation. This information can help in identifying potential challenges and validating the viability of using the drug in the gel system.

### VARIOUS POLYMERS USED IN NASAL IN-SITU GELLING SYSTEM:

- **[1,3,6,17]Poloxamer: -**

Poloxamers are triblock copolymers with a center block of hydrophobic polypropylene oxide (PPO) flanked by two hydrophilic polyethylene oxide (PEO) blocks. Among this family of copolymers, poloxamer 407 is a non-ionic surfactant with reversible gelation properties above a particular polymer concentration and a particular temperature. The gelation phenomenon is reversible and characterized by a sol-gel transition temperature ( $T_{sol-gel}$ ). Below  $T_{sol-gel}$ , poloxamer407 aqueous solutions remain fluid and the solution turns to a semi-solid material above this temperature which is shown in Fig 7. The thermogelation is due to hydrophobic interactions between the poloxamer 407 copolymer chains. By elevating the temperature, the poloxamer 407 copolymer chains start to aggregate into a micellar structure. The formation of micelle structures is a result of the dehydration of the hydrophobic PPO repeat units and defines the initial step of gelation.  $T_{sol-gel}$  is concentration dependent and increases by a reduction of the poloxamer 407 concentration in aqueous solution until a lower level is reached at which point poloxamer 407 does not gel anymore.

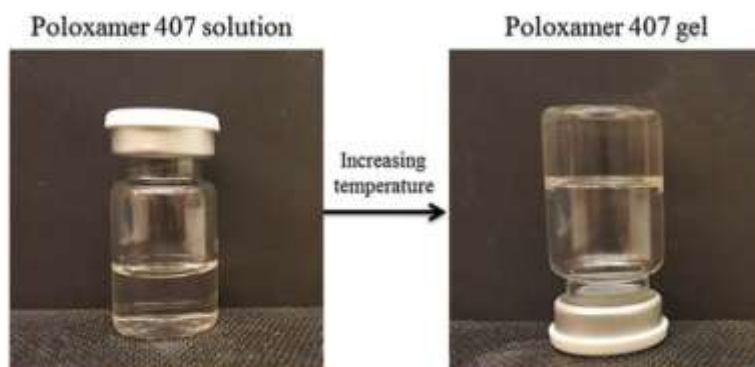


FIG 7: [3]SOL GEL TRANSITION OF POLOXAMER 407

- [1,18]**Chitosan:**

Chitosan, an amine-polysaccharide is a pH-dependent, cationic polymer. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel-like precipitate. Adding poly salts, bearing a single anionic head, like glucose phosphate salts to chitosan aqueous solution can transform the cationic polysaccharides solution into a thermally sensitive pH-dependent gel.

- [1,4,18]**Pectin:**

Pectins are a family of polysaccharides. Low methoxy pectins readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains. Although the gelation of pectin will occur in the presence of H<sup>+</sup> ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery.

- [4,5]**Gellan gum :**

Gellan gum is an anionic deacetylated, exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit of 1b-l-rhamnose, 1b D-glucuronic acid, and 2b D-glucose. The mechanism of gelation involves the formation of double-helical junction zones followed by aggregation of the double-helical segments to form a 3-D network by complexation with cations and hydrogen bonding with water. Because human nasal mucosa is covered with approximately 0.1 ml mucus, which consists of sodium, potassium, and calcium ions.

- [5,6,20]**Carbopol:**

Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol-to-gel transition in an aqueous solution as the pH is raised above its pka of about 5.5. Carbopol (poly acrylic acid) is a well-known pH-dependent polymer, which stays in solution form at acidic pH. but forms a low-viscosity gel at alkaline pH.

- [21]**Ethyl (Hydroxyethyl) Cellulose :**

Ethyl (hydroxyethyl) cellulose (EHEC) is a non-ionic amphiphilic polymer that contains both hydrophobic and hydrophilic structural units. It shows macroscopic phase separation when the temperature is raised above the lower critical solution temperature (LCST), as a result of the intermolecular aggregation of hydrophobic domains. EHEC is water-soluble due to the presence of hydrophilic segments in greater amounts than hydrophobic units. Semi-dilute aqueous solutions of a certain type of EHEC have been shown to exhibit thermogelling properties in the presence of ionic surfactants.

[6]**PROPERTIES OF NASAL IN-SITU GEL :**

- It should have a long residence time.
- It should be low viscous.
- Free-flowing allows for reproducible administration to the nasal cavity.
- The nasal in-situ gel follows a phase transition mechanism and shear forces in the nasal cavity wall.

[1]PROFILE AND IDEAL DRUG CANDIDATE SUITABLE FOR NASAL DRUG DELIVERY SYSTEM:

PROFILE OF AN IDEAL DRUG CANDIDATE SUITABLE FOR NASAL DRUG DELIVERY SYSTEM

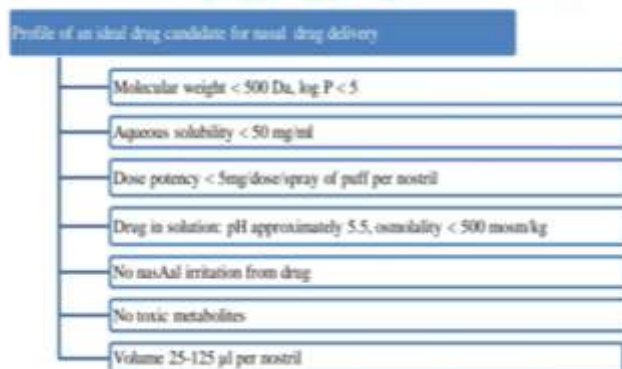


FIG 8

[9,22,23]EVALUATION PARAMETERS FOR NASAL IN-SITU GELLING SYSTEMS -

PARAMETERS	OBSERVATION
1. Clarity	The clarity of in situ gel is found by visual inspection under the black and white background.
2. Texture analysis	The firmness, consistency, and the cohesiveness of formulation may be determined using a texture analyser which mainly indicates the syringe the ability to sol so the formulation can easily be administered in-vivo.
3. In vitro drug release studies	For in-situ formulations to be administered orally, ocular, or intranasally the drug release studies are carried out with plastic dialysis cells. Further studies are performed using analytical methods.
4. Sterility testing	Sterility testing is carried out as per the IP 1996. incubate the formulation for not less than 14 days at 300°-350°C in the fluid thioglycolate medium to find the growth of bacteria at 200°-250°C in Soybean casein digest medium to find the growth of fungi in the formulation.
5. Accelerated stability studies	Formulation is replaced in an amber-colored vial and sealed with aluminum foil for short-term accelerated stability at 40±20°C and 75±5% RH as per ICH state guidelines.

6.	Appearance	In situ, the nasal gel is examined visually for clarity in sol and gel form.
7.	pH of the gel	With the help of a pH meter pH of the in situ nasal gel is measured.
8.	Critical ionic concentration (cic)	Critical ionic concentration is a crucial parameter for in situ ionic gels, indicating the minimum concentration required for phase transition.
9.	Differential scanning calorimetry	Differential scanning calorimetry is used to detect any interactions between the pure ingredients and excipients by comparing the thermograms.

**CONCLUSION:**

For the development of a nasal in situ gel that is both stable and effective, it is crucial to consider drug-excipient compatibility. The selection of the drug should be based on various factors such as physicochemical properties, therapeutic indications, stability, bioavailability, and compatibility with other excipients. By following these criteria, researchers and pharmaceutical companies can create innovative and effective drug delivery systems that meet the ever-increasing demand for nasal drug delivery. Nasal drug delivery is an exciting field that offers controlled drug delivery for extended periods while bypassing bioavailability issues. Using in situ nasal gels made of polymers provides several advantages over traditional dosage forms and can be considered a controlled-release drug delivery system. Moreover, the use of water-soluble, biodegradable polymers in the development of in situ nasal gel formulations makes them highly favorable.

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