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Review Article

A Review on Nasal In- Situ Gel for CNS Targeting

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ABSTRACT

Delivery of drugs to the central nervous system is challenging due to the restrictive nature of the blood–brain barrier. The intranasal route has emerged as a promising non-invasive strategy for direct brain targeting through the olfactory and trigeminal pathways. Nasal in-situ gel systems are particularly advantageous as they are administered as liquids and undergo gelation within the nasal cavity in response to physiological stimuli such as temperature, pH, or ionic strength. This transformation enhances nasal residence time, reduces mucociliary clearance, and provides controlled and sustained drug release, thereby improving drug absorption and bioavailability in the brain. Nasal in-situ gels also offer benefits such as ease of administration, rapid onset of action, improved patient compliance, and reduced systemic side effects. This review highlights the principles, formulation strategies, advantages, evaluation methods, and future potential of nasal in-situ gel systems as an effective approach for CNS drug targeting.

INTRODUCTION

There are a growing number of items that can be administered via the systemic and local administration approach. Recently, in-situ gel has been used as a novel breakthrough dosage form for nasal drug delivery. Nasal in-situ gels are injected into the nasal cavity as a low viscosity solution in compared to liquid nasal formulations. The polymer undergoes a conformational change that results in a gel when it comes into contact with the nasal mucosa. Nasal drug delivery not only prolong the duration of the drug's interaction with the absorptive site within the nasal cavity, but also deliver the medication gradually [1].

Nasal route uses a variety of formulations, including nasal gel, spray, powders, and more. The primary method of administration to attain a quicker and greater extent of medication absorption is the transmucosal route of drug delivery, which includes the mucosal lining of the nasal, rectal, vaginal, ocular, and oral cavities. This is because of the nasal passages physiology

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and anatomy, which include a porous endothelium membrane, a wide surface area, high total blood flow, avoidance of first pass metabolism, and easy accessibility.[2].

Gels are a condition of transitional matter that contains dependable substances (semi-liquids or semi-solids) as well as liquid. Gels combine the diffusive transport features of fluids with the cohesive qualities of solids In situ gels are solutions or suspensions that transform into a gel at the target site due to changes in conditions such as pH, temperature, or ionic concentration. After gel formation, they adhere to the mucosa and provide sustained drug release, helping maintain a steady plasma drug level and prolonging the drug's residence time.[3].

Intranasal drug delivery offers a direct route to the central nervous system via intra- and extraneuronal pathways. This improves drug availability in the brain, allowing lower doses and reducing systemic side effects. It also enables targeted delivery to the brain while limiting exposure to other organs, leading to fewer off-target effects. Moreover, this method provides a rapid therapeutic response, making it suitable for treating acute conditions.[4]

The blood-brain barrier, which restricts drug access to the brain, is the main obstacle to CNS drug delivery. Drug diffusion from the blood into the brain is mostly dependent on the biologically active molecule's capacity to pass through lipid membranes. The second barrier that prevents systemically delivered drug molecules from entering the central nervous system is the blood-cerebrospinal fluid (BCB) barrier. The plexus of the choroid contains the BCB's epithelium. It is set up to restrict how many chemicals and cells can enter the CSF. Proteins and peptides are examples of macromolecular medications that are too big and hydrophilic to cross the blood-brain barrier.[5]

Nasal administration is a systemic route of administration that minimizes the potential of undesirable side effects while fostering high bioavailability and rapid drug absorption; these characteristics, along with its ease of use, have led to growing interest in intranasal drug delivery techniques (Landis et al., 2012). Studies have demonstrated that certain drugs can be given intranasally, bypassing the blood-brain barrier to enable drug access into the brain. This offers an effective way of brain-targeted drug delivery because there is a direct anatomical link between the nasal cavity and the brain.[6]

Due to their high permeability the nasal route show only smaller molecular weight drugs the absorption will be more. For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane so the drugs cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier.[2]

Gel

The transitional condition between the solid and liquid phases is called gel. The liquid phase is immobilized by the solid component, which consists of a three-dimensional network of interconnected molecules. [7]

In-situ gel

The Latin term "in situ" means "in position." It is described as a liquid formulation that, upon administration, produces a solid or semisolid depot. Systems which transform into a gel phase when exposed to physiological variables are referred to as in situ gel forming systems. The early 1980s saw the first suggestion of this novel idea. Cross-linking of polymer chains, which can be accomplished by the production of covalent or non-covalent bonds, is how gel formation happens.

In situ gels were created using both synthetic and natural polymers. Sustained, relatively constant plasma profiles can be produced via in situ gel devices. [7]

Profile of an 'ideal' drug candidate for nasal Delivery An ideal nasal drug candidate should possess the Following attributes(7,8)

1. Low Aqueous Solubility is crucial for delivering the desired dose through 25–150 ml of formulation administered per nostril.
2. Must have suitable nasal absorption characteristics.
3. Should be free from causing any nasal irritation.
4. There should be a sound clinical justification for using nasal dosage forms, such as rapid onset of action.
5. Dosages should typically be low, generally under 25 mg per dose.
6. No harmful nasal metabolites should be produced.
7. The drug should not have any unpleasant odors or aromas.
8. Stability characteristics must be appropriate to ensure efficacy.

Advantages of Nasal In-Situ gel[9,10]

1. Prolongs the retention time of the drug within the nasal cavity.
2. Reduces the need for frequent dosing.
3. Provides fast drug absorption and a quicker onset of therapeutic action.
4. Prevents drug degradation in the gastrointestinal tract caused by acidic conditions or digestive enzymes.
5. Requires a smaller dose to achieve the desired effect.
6. Helps reduce both local and systemic adverse effects.
7. Enhances the overall bioavailability of the drug.
8. Enables direct delivery to systemic circulation and the central nervous system (CNS).
9. Decreases the chance of overdose for drugs acting on the CNS.
10. Promotes better patient acceptance and compliance.

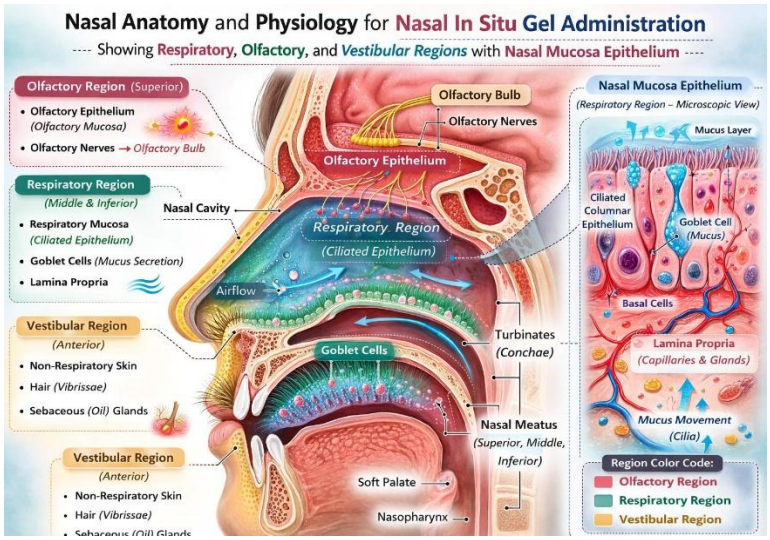
Disadvantages of Nasal In-Situ gel [9,10]

1. The drug transport mechanism is not completely understood.
2. The nasal cavity has a smaller surface area compared to the gastrointestinal tract (GIT).
3. Only a limited volume of formulation can be administered through the nasal route.
4. This route is more appropriate for highly potent drugs.
5. Drug loss may occur due to mechanical or technical factors during administration.
6. There is a possibility of damage to the nasal mucosa.
7. Irritation of the nasal mucosal lining may occur.
8. In some cases, permanent damage to the cilia of the nasal mucosa may result.

Anatomy and Physiology of Nose :

The human nasal cavity consists of two passages separated by the nasal septum and is divided into three main regions: the vestibular region, the respiratory region, and the olfactory region. The total surface area of the nasal cavity is approximately 150–160 cm^2, with a total volume of around 20 mL, while only about 200 µL is typically available for drug administration.

The nasal vestibule is located at the entrance of the nasal cavity and primarily acts as a protective filtering region. Nasal hairs present in this area help trap dust and other harmful particles, preventing them from entering deeper parts of the respiratory tract.The respiratory region forms the largest part of the nasal cavity, covering nearly five-sixths of the nasal mucosal surface. It contains highly vascularized mucous membranes, which make it an efficient site for drug absorption into the systemic circulation. [11]



Cilia are tiny hair-like structures present on the surface of the nasal epithelium, with nearly 300 cilia found on each epithelial cell. These structures significantly increase the surface area available for drug absorption. Their coordinated, wave-like motion helps move trapped particles toward the throat, where they can be swallowed. Below the epithelial layer lie several important components, including blood vessels, nerves, serous glands, and secretory glands. A dense capillary network is also present in this region, which plays a significant role in the absorption of drugs into systemic circulation. The epithelial surface is covered by a mucus layer that is continuously renewed approximately every 10–15 minutes. The pH of this mucus typically ranges between 5.5 and 6.5 in adults, while in younger individuals it varies from about 5.0 to 6.7. This mucus layer captures foreign particles, which are then transported and cleared by the ciliary movement within roughly 20 minutes.[2]

The nasal cavity is symmetrically divided by the middle septum into two halves, each of which opens at the face through the nostrils and extends posteriorly to the nasopharynx. These symmetrical halves can be classified into four areas, including the nasal vestibule, atrium, respiratory region, and olfactory region, each distinguished by their unique anatomical and histological characteristics.[7]

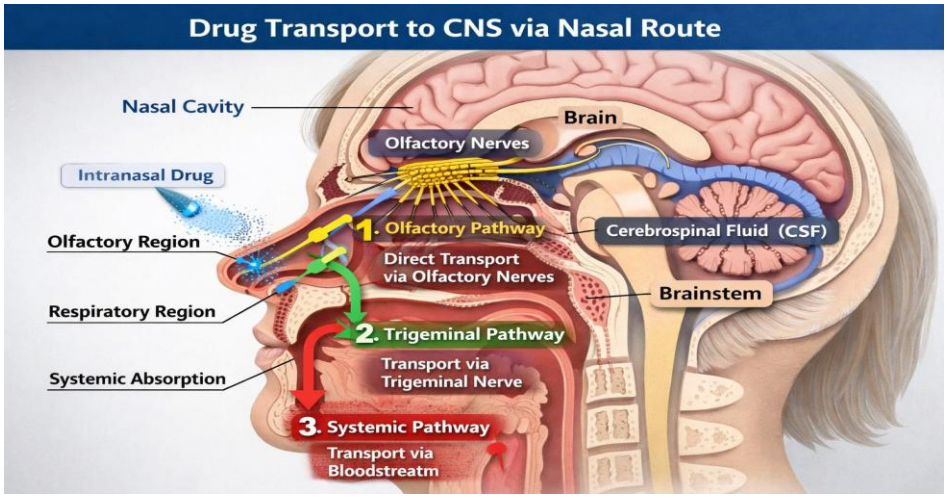
The Respiratory region-The respiratory region, the largest and most blood-rich area of the body, is essential for the absorption of drugs into the bloodstream. This region consists of four main cell types: basal cells, goblet cells, and both non-ciliated and ciliated columnar cells. These cells are key players in various transport processes, enabling the exchange of ions and water. Additionally, the cilia on these cells help with movement and play a vital role in keeping the mucosa hydrated by trapping moisture.(12,13)

The olfactory region- Its width measures about 10 cm^2, playing a crucial role in delivering medication to the brain and cerebrospinal fluid (CSF). The olfactory region is located just below the cribriform plate at the ceiling of the nasal cavities. The ethmoid bone separates the nostril canals from the cranial chamber. Notably, the nasal mucosa often appears yellow, contrasting with the surrounding pink tissue. While primarily responsible for breathing, the nostrils serve a vital function in humans.[12,13]

3. The Vestibular region- The nasal cavity's front section has a surface area of 0.6 cm^2 and is lined with stratified squamous keratinocytes that contain sebum glands. This area marks the beginning of the nasal passages and plays a crucial role in filtering out airborne pollutants. Despite the difficulties associated with drug assimilation in this region, it exhibits considerable resistance to the surrounding hazardous environment. However, when it comes to drug absorption, this area is typically considered the least significant of the three primary regions.[12,13]

The pathways through which Drugs can enter the brain through The nose

Olfactory nerve pathway



1. Olfactory nerve pathway

The olfactory nerve pathway is recognized as a critical route for drug delivery into the brain from the nasal cavity, offering a unique way to bypass the blood-brain barrier (Ruigrok and de Lange, 2015). After intranasal administration, drugs can reach the olfactory mucosa (olfactory epithelium), which contains olfactory receptor neurons responsible for signal transduction. Drug molecules reach these neurons through paracellular or transcellular pathways, aided by the structure of the nasal epithelium and its junctions.From there, the drug travels along the olfactory nerves, passes through the cribriform plate, and reaches the olfactory bulb on the brain surface. The drug may also enter the cerebrospinal fluid (CSF) and distribute throughout the brain.This pathway enables drug delivery to deeper brain regions such as the cortex, cerebrum, and cerebellum.[14]

Drug transport across the olfactory epithelium occurs through three main pathways[15]

a)The transcellular pathway involves movement through sustentacular cells, mainly by passive diffusion or endocytosis, and is commonly used by lipophilic drugs.

b)The paracellular pathway occurs between sustentacular cells and mainly allows the passage of hydrophilic drugs, with absorption depending on the drug's molecular weight; drugs up to about 1000 Da can achieve good bioavailability, especially with absorption enhancers.

c)the olfactory nerve pathway, where drugs are taken up into neuronal cells by endocytosis and then transported to the olfactory bulb through intracellular axonal transport

2. Trigeminal nerve pathway

The trigeminal pathway involves drug transport through branches of the trigeminal nerve that supply the nasal respiratory mucosa, including the ethmoidal nerve (from the ophthalmic division) and the posterior nasal and nasopalatine nerves (from the maxillary division). These nerves connect to the trigeminal ganglion and further project to nuclei in the brainstem.Studies show that substances administered intranasally can reach the trigeminal nerve. Some sensory neurons in the nasal epithelium may also extend directly to the olfactory bulb. Both intracellular axonal transport and extracellular movement through perineural spaces contribute to drug delivery to the brain through this pathway.[16]

3. Blood circulation pathway

Low-molecular-weight lipophilic drugs predominantly enter The brain following absorption into the general circulation through The rich capillary network in the lamina propria of the respiratory Region. However, after entering the general circulation, drugs must Cross the BBB to reach the CNS; thus, this pathway is a limiting Factor in the therapeutic application of many drugs (Illum, 2000).Following nasal administration, a drug will eventually reach The CNS through one or more of the aforementioned pathways With differences in drug properties, formulations, and routes Of administration dictating the dominant pathway of a drug Delivery system.[6,17]

Mechanism of Drug Absorption by Nasal Route

The absorbed drugs from the nasal cavity must pass through The mucus layer. It is the first step in absorption. Small, Unchanged drugs easily pass through this layer but large, Charged drugs are difficult to cross it. The principle protein Of the mucus is mucin which has the tendency to bind to the Solutes, hindering diffusion. Additionally, structural Changes in the mucus layer are possible as a result of Environmental changes.

The two mechanisms that include there:

First mechanism-It involves an aqueous route of transport, Which is also known as the paracellular route but slow and Passive. There is an inverse log-log correlation between Intranasal absorption and the molecular weight of water Soluble compounds. The molecular weight greater than 1000 Daltons show poor bioavailability.[19]

Second mechanism-It involves transport through a lipoidal Route known as the transcellular process. It is responsible For the transport of lipophilic drugs that show a rate Dependency on their lipophilicity. Drugs can also cross cell Membranes by an active transport route via carrier-Mediated means or transport through the opening of tight Junctions. For example chitosan, a natural biopolymer from Shell fish opens tight junctions between epithelial cells to Facilitate drug transport.[19] This process can happen through either non-specific or receptor-mediated endocytosis, but current research suggests that non-specific binding and uptake are significantly more prevalent. Once inside an endosome, the substance is transported through the Golgi network and along axonal pathways to reach the synapse, which could be in the olfactory bulb for the

olfactory nerve or in the pons for the trigeminal nerve.[18]

METABOLISM OF DRUGS IN NASAL CAVITY

Enzymes are known to exist in the nasal cavity, but they do Not appear to have a significant effect on the extent of Absorption of most of the compounds except proteins and Peptides. Drugs may show maximum absorption and higher Bioavailability in the nasal cavity, which may be attributed to

The following reasons : [9]

1. The rate of absorption is very fast rendering very Short exposure time of the drugs to the enzymes, And
2. The level of enzymes in the nasal tissue (mg /g) is Very low and can be easily saturated with the drug

APPROACHES OF IN SITU GELLING SYSTEM

There are 4 mechanisms for triggering the in situ Gelling formation of biomaterials. These include:

1. In situ gel formation due to physiological Stimuli:

a) Temperature triggered in situ gel systems
b) pH triggered in situ gelling systems

2. In situ gel formation due to ion-activated System
3. In situ gel formation due to physical Mechanism

a) Swelling
b) Diffusion

4. In situ gel formation due to chemical reactions

a) Ionic cross-linking
b) Enzymatically cross linking
c) Photo-polymerization

1. In situ gel formation due to physiological Stimuli:

There are some polymers which undergo large And unexpected physical and chemical changes In response to small external changes in their Environmental conditions. Such polymers are Called Stimuli-responsive polymers. They arealso called as stimuli-sensitive, intelligent, smart Or environmentally sensitive polymers. These Polymers recognize a stimulus as a signal, judge The degree of the signal and then transform their Chain confirmation in response.[6]

a) Temperature triggered in situ gel system

Temperature-sensitive polymers are a widely researched category of environmentally responsive systems in drug delivery due to their ease of temperature control and applicability in both in vitro and in vivo environments, forming gels upon temperature changes to sustain drug release, with various strategies available for engineering these thermosensitive systems.

Three main strategies are used in engineering the Thermosensitive sol-gel polymeric system. Hence they are classified into

- Negatively thermosensible, which contract Upon heating
- Positively thermosensible, which contract Upon cooling
- Thermally reversible gel

Polymers which show temperature induced Gelation are poloxamers/pluronics, cellulose

Derivatives [HPMC, ethyl (hydroxy ethyl) Cellulose (EHEC), methyl cellulose], Xyloglucan, tetronics, etc.[20]

b) pH-Induced In-Situ Gelling System:

Polymers that possess acidic or alkaline functional groups and respond to pH changes are known as pH-sensitive polymers. The pH level serves as a crucial signal, which can be effectively utilized through pH-responsive materials. The gelling process of the solution is initiated by fluctuations in pH. At a pH of 4.4, the formulation exists as a freely flowing solution, which transitions into a gel-like state when the pH is elevated to 7.4, mimicking the body's fluid environment. Notable polymers that exhibit this pH-induced gelation include cellulose and its derivatives, polyvinyl acetate, and polyethylene glycol[21]

2.In situ gel formation due to ion-activated System

In ion-activated in situ gelation, the presence of monovalent and divalent cations such as Ca2+, Mg2+, K+, and Na+ in nasal secretion causes the phase transition of the anionic polysaccharide gellan gum.[22]

3.In situ gel formation due to physical Mechanism

a) Swelling

In situ formation can take place when a material absorbs water from its surroundings, causing it to expand and fill the desired space. An example of such a substance is myverol 18-99 (glycerol mono-oleate), which is a polar lipid that swells in water to create lyotropic liquid crystalline phase structures. This compound possesses some bioadhesive properties and is capable of being broken down in vivo through enzymatic processes.[23]

b) Diffusion

This technique entails the migration of solvent from a polymer solution into the adjacent tissue, leading to the precipitation or solidification of the polymer matrix. N-methyl pyrrolidone (NMP) has been identified as an effective solvent for this type of system.[23]

4.In situ gel formation due to chemical reactions

a) Ion cross-linking

Polymers can experience phase transitions when exposed to different ions. Certain polysaccharides belong to the group that is sensitive to ion presence.[20]K-carrageenan produces rigid and brittle gels when exposed to small amounts of K+, while i-carrageenan creates more elastic gels, particularly with the presence of Ca2+. Gellan gum, sold under the trademark Gelrite®, is an anionic polysaccharide that gels in the presence of various mono- and divalent cations, such as Ca2+, Mg2+, K+, and Na+. For low-methoxy pectins, gelation is typically triggered by divalent cations, especially Ca2+. Similarly, alginic acid can gel when it interacts with divalent or polyvalent cations like Ca2+, thanks to its connection with glucuronic acid blocks within the alginate chains.[24]

b.Enzymatic Cross-Linking

Researchers are exploring innovative delivery systems that utilize hydrogels capable of releasing insulin in response to stimuli. These systems incorporate cationic, pH-sensitive polymers that contain immobilized insulin and glucose oxidase. When blood glucose levels rise, the hydrogels can swell, allowing insulin to be released in a controlled, pulsatile manner. [23]

The in situ formation of materials using natural enzymes is an area that hasn’t been explored extensively but offers distinct advantages compared to traditional chemical and photochemical methods. One notable benefit is that enzymatic processes can function effectively under physiological conditions, eliminating the need for potentially harmful substances like monomers and initiators. [24]

4. Induced photo polymerization gelation

Induced photo polymerization gelation refers to a widely used technique for the in situ formation of biomaterials. By injecting a solution that contains monomers or reactive micromers along with an initiator directly into a targeted tissue area, electromagnetic radiation can then be applied to create a gel. This photo reaction occurs rapidly, enabling polymerization at physiological temperatures. Once the photo polymerization systems are administered via injection, they undergo photo curing in the specific location with the aid of fiber optic cables, subsequently releasing the drug over an extended period.[25]

❖ Factors Influencing Nasal Drug Absorption

A)Physicochemical Properties of Drug[26]

1) Molecular weight and size

The absorption of hydrophilic drugs via the nasal route is optimal for molecules up to 1000 Daltons, with significant reductions for larger sizes unless penetration enhancers are used, while a linear relationship between the percentage absorbed and molecular weight suggests the involvement of aqueous channels, noting that particles over 10 µm settle in the nasal cavity, those between 2 and 10 µm reach the lungs, and particles smaller than 1 µm are exhaled.

2)Solubility and dissolution

Drug solubility significantly impacts how well a drug is absorbed through biological membranes, as particles in the nostrils or those cleared from the nasal cavity may not be absorbed effectively.

3)Chemical form

The chemical form of a drug at the nasal mucosa significantly influences its absorption, as altering it to a salt or ester form can change how well it is taken up.

4)Partition coefficient and pKa

The relationship between the partition coefficient and nasal absorption is consistent, as the pH partition theory indicates that unionized species are absorbed more effectively than their ionized counterparts.

B)Nasal effect factors[27]

1)Membrane permeability

Nasal membrane permeability is crucial for drug absorption via this route, but water-soluble and larger molecules, like peptides and proteins, typically exhibit lower permeability and are absorbed primarily through endocytotic transport in limited quantities (Inagaki, 1985).

2)Environmental pH

Environmental pH significantly impacts nasal drug uptake, as demonstrated by compounds like benzoic acid and salicylic acid, which are absorbed most effectively in their nonionized forms at specific pH levels (Franz and Oth 1993).

3)Mucociliary clearance

Mucociliary clearance in the upper respiratory tract serves to keep harmful substances like allergens, bacteria, viruses, and toxins from entering the lungs by trapping them in mucus and moving them toward the nasopharynx for eventual expulsion into the gastrointestinal tract (Armengot 1990).

4)Cold, Rhinitis

Rhinitis, a common condition often linked with colds, affects drug bioavailability and is primarily categorized into allergic and non-allergic types, with symptoms like excessive mucus production, itching, and sneezing caused by viruses, bacteria, or irritants.

C) Effect of drug formulation

1) Viscosity

As formulation viscosity increases, it can enhance the contact time and potential absorption of drugs in the nasal mucosa, but in some cases, like with metoclopramide hydrochloride, higher viscosity can lead to reduced drug absorption due to decreased diffusion, though it may also extend the therapeutic period for nasal formulations.[28]

2)pH

The absorption of drugs through the nasal mucosa is influenced by the pKa of the drug, the pH at the absorption site, and the formulation's pH, which should ideally align with the natural nasal mucosa range of 5.0-6.5 to minimize irritation while maximizing the presence of non-ionized drug species and inhibiting bacterial growth.[28]

3) Pharmaceutical Excipients -

The use of excipients such as absorption enhancers, mucoadhesive polymers, and enzymatic inhibitors in drug formulations enhances drug absorption, but their selection must consider the physiological properties of the nasal cavity and the characteristics of the drug to achieve optimal therapeutic outcomes.[29]

4) Buffer capacity

Nasal formulations, typically delivered in volumes of 25 to 200 mL, may have their pH altered by nasal secretions, making a suitable buffer capacity essential to maintain the pH for optimal drug absorption (Joshi et al. 2014a).[30]

❖ Method of Preparation For in situ gel

1)Cold method –

In the cold method, double distilled water and the product are mixed in a refrigerator at 4 ºC overnight, after which the gelling polymer, such as poloxamer, chitosan, or Carbopol, is gradually added while stirring, and the dispersion is kept in the refrigerator until a clear solution is obtained and adjusted.[31]

This method is chosen when employing poloxamer, chitosan, or carbopol as a gelling polymer. The polymeric dispersion of poloxamer is in solution at lower temperatures and turns into a gel at higher nasal temperatures because the solubility of the polypropylene oxide chain in poloxamer diminishes at high temperatures, inducing precipitation or salting-out of a polymer. Similarly, chitosan requires a low temperature to remain in solution at room temperature due to its hydrophobicity.[32]

1. Hot method

This approach is preferred when using gellan gum or pectin as the gelling polymer. Gellan chains dissolve in water at higher temperatures and take on a random coil confirmation with high segmental mobility.[30]When gellan gum solution is cooled in the presence of ions like K+ or Ca2+, sol-gel transition takes place. In a similar vein, pectin requires a greater temperature for demethoxylation, which facilitates the formation of a solution or the dissolution of pectin.[31]

EVALUATION PARAMETERS F NASAL IN SITU GELS

1. Clarity: The clarity of the formulation will be assessed by visually examining it against both black and white backgrounds[33]
2. Viscosity: Using artificial tissue fluid and several types of viscometers, including as the Brookfield viscometer and the cone and plate viscometer, the viscosity and rheological properties of the polymer formulation can be evaluated in solution or gel.[34]

3. Texture Analysis -A texture analyser is used to evaluate the formulation's cohesiveness, stiffness, and consistency. This mostly shows how easily the formulation may be delivered in vivo.[35]
4. Drug Content Analysis- A total of 1 ml of the formulation was transferred into a 10 ml volumetric flask. This was then diluted with 10 ml of distilled water, adjusting the total volume to 10 ml. From this solution, 1 ml was taken and further diluted with distilled water to a final volume of 10 ml. The absorbance of this prepared solution was subsequently measured at the specific wavelength of the drug using a UV-visible spectrophotometer.[35]
5. Gel Strength Assessment To evaluate gel strength, a rheometer is employed. Begin by preparing a specific volume of gel from the sol form in a beaker, which varies according to the process of the gelling agent. As the beaker is raised at a consistent pace, it's essential to gently insert a probe into the gel. The depth at which the probe penetrates the gel surface provides insights into the changes in load experienced by the probe.[36]
6. Gelling Temperature - This test focuses on the thermosensitive in situ gel. To begin, 2 ml of the in situ gel was placed in a test tube and immersed in a water bath. The temperature of the water bath was gradually and consistently increased. After allowing the gel to equilibrate at each temperature setting for five minutes, we checked the formulation for signs of gelation. Gelation is confirmed when the meniscus remains stable and does not shift when the test tube is tilted to a 90° angle.[36]
7. Research on Drug Excipient Interactions – Fourier Transform studies are used to investigate the interactions between drugs and polymers. Using infrared spectroscopy, we assessed both the purity of the drug sample and its interactions with various polymers. We gathered infrared spectra of the drug and polymers individually, as well as in combination. Following this, we analyzed the spectra for any indications of interactions by comparing them with the standard IR spectra of the pure drug and the interaction profile between the drug and polymer.[37]
8. In Vitro Diffusion Studies or Ex vivo permeation studies
9. The nasal diffusion cell is a glass apparatus with a 60 ml water-jacketed recipient chamber and a 3 mm flanged top. Its lid has three openings for sampling, a thermometer, and a donor tube. The donor chamber is 10 cm long with a 1.13 cm internal diameter, also holding 60 ml and having similar openings. Sheep nasal mucosa is carefully separated from bone, washed with distilled water containing gentamicin, and placed on the donor chamber so it contacts the diffusion medium. Samples of 0.5 ml are taken from the recipient chamber at set intervals and stored in amber ampoules while maintaining the temperature at 37 °C.[38]
10. Spreadability Assessment -To evaluate spreadability, we utilized a rectangular glass slide measuring 10 × 4 cm. The sheep nasal mucosa was carefully secured onto the slide with a thread attached to the serosal side. Next, the slide was placed in a hot air oven set at 37 °C, where we applied a drop of gel onto the mucosa at an angle of 120°. We assessed the spreadability by measuring how far the gel drop traveled before it started to gel. The average distance from three separate trials was recorded for analysis. [39]
11. In vitro drug release

    An in vitro drug diffusion study was conducted to assess various formulations using a Franz diffusion cell (Gowda et al., Citation2011). A dialysis membrane with a molecular weight cut-off of 12,000–14,000 kDa served as the

diffusion barrier. Prior to the experiment, the dialysis membrane was soaked in phosphate buffer at pH 6.4 for 24 hours. The diffusion cell was then filled with 21 ml of phosphate buffer at pH 6.4, and the dialysis membrane was mounted onto the cell. A gel containing a drug equivalent to 10 mg was applied to the donor chamber. The temperature was carefully regulated between 32°C and 34°C using a circulating water bath. At various intervals, 1 ml samples were taken, replaced with an equal volume of fresh solution, filtered, and the drug concentration was measured using a UV-visible spectrophotometer at 226 nm.[40]

12. Nasal Ciliotoxicity Studies
    Nasal ciliotoxicity of the optimized formulation (D7) was evaluated ex vivo using sheep nasal mucosa following institutional ethical guidelines. Three equal mucosal samples (A, B, and C) were placed in Franz diffusion cells. Sample A was treated with phosphate buffer (negative control), sample B with isopropyl alcohol (positive control), and sample C with 0.5 mL of the optimized darunavir nasal in situ gel (D7). After 6 hours, the tissues were washed with nasal saline and subjected to histopathological examination using hematoxylin–eosin staining. The slides were observed under a ZEISS Axioscope 5 light microscope at 400× magnification, and images were recorded using an attached camera.[41]
13. Accelerated stability studies:Accelerated stability studies were conducted according to ICH guidelines. The formulation was stored in aluminum-sealed amber vials, and if any vial failed, the formulation was temporarily replaced. The study conditions were maintained at 40 ± 2 °C temperature and 75 ± 5% relative humidity.[33]

CONCLUSION:

Nasal in-situ gel systems represent a highly promising and innovative platform for targeted drug delivery to the central nervous system. By exploiting the intranasal pathway, drugs can directly reach the brain via olfactory and trigeminal routes, effectively bypassing the blood–brain barrier and improving therapeutic efficiency. The in-situ gelation mechanism enhances nasal residence time, reduces mucociliary clearance, and enables controlled and sustained drug release. These systems also offer advantages such as non-invasive administration, improved bioavailability, and better patient compliance. Despite certain formulation challenges, continuous advancements in polymers and delivery strategies are expected to further enhance their potential, making nasal in-situ gels a valuable and future-oriented approach for effective CNS drug targeting.

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