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A Review On In Situ Nasal Gels For Nasal Drug Delivery System

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ABSTRACT

The most popular method for giving the medication orally to the body is the oral route. Some restrictions, including inadequate bioavailability, first-pass hepatic metabolism, medication targeting to specific organs, and drug absorption, might make oral delivery challenging. As a result, parenteral, transmucosal, and transdermal routes are recommended over oral ones. Because the intranasal route's temporal profile of drug concentration is similar to that of the intravenous route, it is considered a favourable approach. An innovative method of medicine administration, the in situ nasal drug delivery system, has been developed to improve patient safety and effectiveness. The medication is delivered as a low viscosity solution using in situ nasal gels. When the nasal mucosa comes into touch with it, The polymer undergoes a transformation into gel form. For medications whose oral administration is troublesome because of gastrointestinal discomfort, poor drug absorption, low drug bioavailability, and first-pass hepatic metabolism, the gel formulation via nasal route is suitable. The gel formulation uses a variety of triggered polymers. The current study concentrated on the following topics: commercialised in situ nasal gel products, therapeutic considerations, nasal cavity architecture and physiology, possibilities and problems in nasal drug administration, and numerous assessment factors taken into account during in situ gel manufacture.

KEYWORDS: In-situ gel, nasal mucosa, Bioavailabilty, novel dosage form, first pass metabolism Mucoadhesive Drug Delivery System

Introduction [4]

One of the best methods for administering drugs is orally. Oral bioavailability of some drugs has encouraged the search for a more efficient systemic delivery route where systemic effects are envisaged [1] .In the transmucosal route of drug delivery, the nasal mucosa is the primary route of administration to achieve a greater and quicker amount of drug absorption [1]. One particularly promising delivery method has been transmucosal nasal administration. Comparing the nasal route to the oral route, it has been demonstrated that several medications have greater systemic bioavailability[2] .In the Indian ayurvedic medicine systems, nasal route One well accepted therapy method is called NASYA KARMA. It is a practical way to administer medications that have a low oral bioavailability and are only effective in modest dosages. For self-medication, it is the best dose form. [2]

A practical option for the systemic and local delivery of a variety of medicinal substances is intranasal administration. In order to maximise patient convenience, comfort, and compliance, the nasal mucosa's vast surface area allows for a speedy start of effects, the possibility of direct administration to the central nervous system, avoidance of first pass metabolism, and non-invasiveness[3].Therapeutic substances with a large molecular weight, such proteins and peptides, are prevented from passing through the nasal mucosa. It is possible to safely and reversibly open the tight connections that make up this barrier to paracellular medication transport. Intranasal therapy is non-invasive, painless, and does not require sterile preparations. It may also be easily and quickly delivered by the patient, for example, in an emergency [4-6].

The use of intranasal microemulsions, gels, and microspheres to provide proteins and peptides via the nose route has grown in recent years [2].In situ gel is a novel nasal medication delivery dosage type that was just released. In contrast to in situgels, liquid nasal formulations are injected into the nasal cavity as low viscosity solutions. The polymer transforms into a gel upon contact with the nasal mucosa. in order to gradually release medications into the nasal cavity while also lengthening the duration of interaction between the drug and the absorption site.[7]

- Advantages

- Nasal drug administration is one way to get medications that are not absorbed when taken orally into the bloodstream.
- It avoids hepatic first pass metabolism.
- Rapid onset of action.
- In contrast to parenteral approaches, self-medication is made easier by easy accessibility and needle-free drug administration that eliminates the requirement for trained staff, enhancing patient compliance.
- There is no drug breakdown in the gastrointestinal system.
- Absorption enhancers and other methods can be used to increase the bioavailability of big medicinal molecules.
- It is possible to obtain a rapid start of action and rapid medication absorption.
- For smaller pharmacological molecules, the nasal bioavailability is good.
- The nasal route is used to provide drugs that have low stability in GIT fluids. Research to date suggests that the nasal route is a substitute for the parenteral route, particularly for medications that contain proteins and peptides.

- Disadvantages

• The absorption surface area of the nasal cavity is less than that of the GIT.

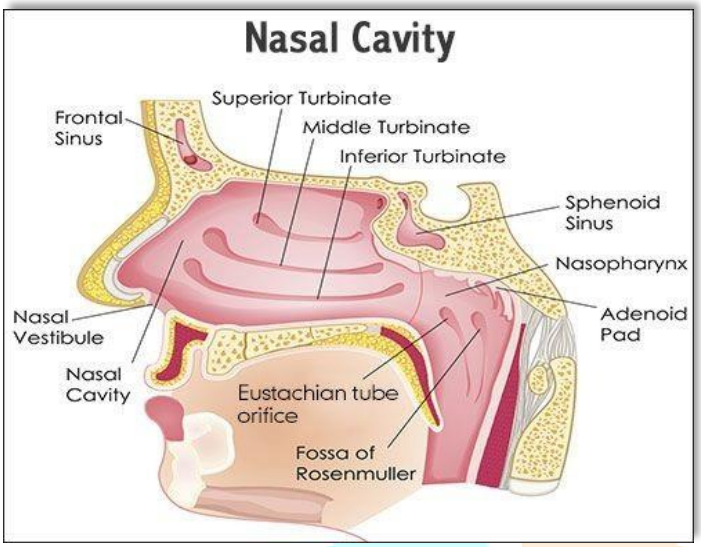
• Compared to oral administration systems, this method is rather uncomfortable for patients since it may cause discomfort.

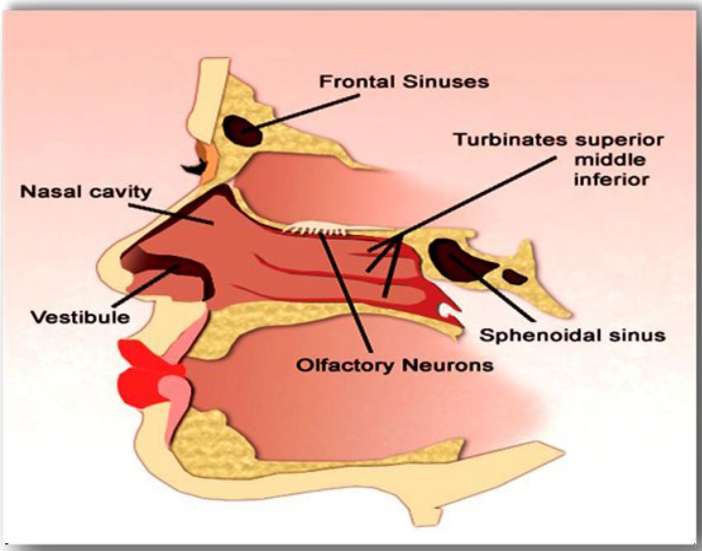
• The substance and the ingredients added to the dosage form carry the danger of local side effects and permanent damage to the cilia on the nasal mucosa.

• Inappropriate delivery strategy may result in a mechanical loss of the dose to other areas of the respiratory system, such as the lungs.

• Difficulty in delivering New drug compounds with high molecular weight or low lipophilicity.

ANATOMY AND PHYSIOLOGY OF NOSE [15]





The septum that separates the nose's two chambers allows it to expand posteriorly to the nasal pharynx. The nasal cavity has a capacity of roughly 15 ml and a surface area of about 150 cm². The vestibular, respiratory, and olfactory regions make up the nose. The vestibule, the most anterior portion of the nasal cavity, opens through the nostrils. The human nose is crucial to the delivery of medications to the brain. The respiratory system is crucial, aside from systemic medication delivery. The respiratory epithelium is composed of rough cells, goblet cells that secrete mucus, and basal cells.[6]Columnar and non-ciliated columnar cells. These cells facilitate active transport processes like as exchange of water, ions between the cells and cilia motility. The cilia are a hair like microvilli that is three hundred in numbers. They supply large surface area for the drug absorption and the movement of cilia is like a wave and it helps to transport the particles to the throat for intake. Below the epithelium the blood vessels, nerves, serous glands, secretory glands are found. There is a presence of capillaries network that is responsible for drug absorption.The epithelium linked by a mucus secretion layer is revived each ten to fifteen minutes. The ph of the mucus secretion ranges from 5.5 to 6.5 and for youngsters it ranges from 5.0 to 6.7. The mucus layer entrapped the particles which are

In Each Section, Three Distinct Zones: [8]

1. The area of respiration:

The biggest and most vascularised area is the respiratory system, which is primarily in charge of systemic medication absorption. The four cell types that make up the respiratory epithelium are goblet cells, basal cells, ciliated columnar cells, and non-ciliated cells. These cells support active transport mechanisms including cilia movement and intercellular water and ion exchange. They could also help keep the nasal mucosa from drying out.

2. Olfactory region:

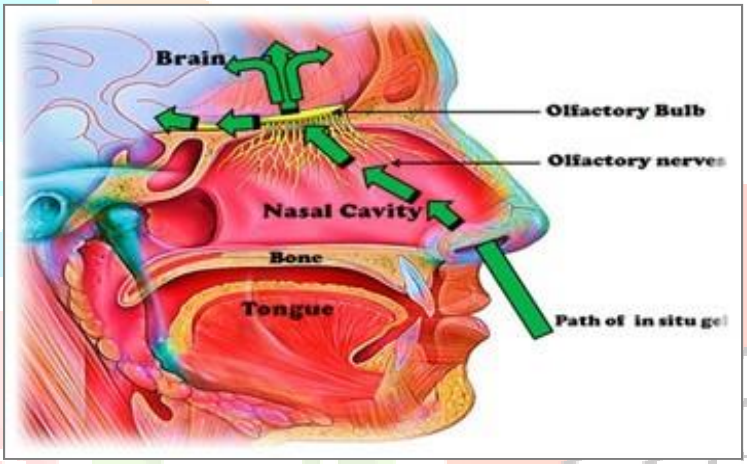
With a surface area of around 10 cm^2, it is essential for the delivery of medications to the brain and cerebrospinal fluid. The nasal cavity's roof is home to the olfactory area. Chambers, directly under the ethmoid bone's cerebral form plate, which divides the cranial cavity from the nasal cavities. Unlike the pink tissue around it, the olfactory tissue is frequently yellow in hue. Three cell types make up the majority of the olfactory epithelium layer: basal cells, subtentacular cells, and olfactory neurone cells.

3. The vestibular region :-

It is situated in the front part of the nasal cavity. The surface's area is 0.6 cm. The nasal area is covered by a stratified squamous keratinised epithelium that contains sebaceous glands. It is located at the opening of the nasal passages and is responsible for filtering out airborne contaminants. It is quite resistant to the damaging environment, despite the fact that medication absorption is very difficult in this region. It is thought to be the least important of

Mechanism of nasal drug delivery [20][21][22]

Since the mucus is simply passed by a tiny, uncharged corpuscle, the first stage in the drug's absorption in the nasal cavity is traversing the mucous membrane. However, the mucous barrier makes it difficult for charged big molecules to flow through. Mucin, a protein found in the mucus layer, binds to solutes to slow down diffusion. Environmental factors, such as variations in ph and temperature, can also trigger structural changes in the mucus layer. [20] simple diffusion, paracellular transport across cells, and transcytosis via vesicle carriers are some of the methods for drug absorption across the mucosa during mucus passage. Prior to entering the systemic circulation, the drug's metabolism depends on the limitations on its absorption.



Duration of stay in the cavity. Although several mechanisms have been put out, the two that follow have received the most attention. The first mechanism uses an aqueous pathway for transfer and is referred to as a paracellular route. This is the passive, sluggish way. The molecular weight of water-soluble substances and intranasal absorption are correlated log-logically. The bioavailability of medications with molecular weights over 1000 Daltons is low.[21] The transport of lipophilic medications that exhibit a rate dependence on their lipophilicity is accomplished by the second mechanism, referred to as a transcellular route, which includes transportation via the lipoid pathway. Active transport via carrier-mediated or tight junction opening allows the medications to pass past the cell membrane.[22]

Methods of formulation of in situ nasal gel:-

Cold method:-

This formulation technique involves mixing the product with a sample amount of double-distilled water in a refrigerator and keeping it there overnight at 4°c. The in situ gelling polymer is then gradually added while being continuously stirred. The dispersion is kept in a refrigerator until a clear solution is created and the volumes are changed. This approach is chosen when formulation calls for gelling polymers such as poloxamer, chitosan, or carbopol. Because the solubility of the propylene oxide chain in poloxamer decreases at high temperatures, causing precipitation or salting from the polymer, concentrated in gel at higher nasal temperatures. Similarly, low temperatures are frequently needed for chitosan to often requires low temperatures to survive as a solution

at room temperature, its hydrophobicity increases with higher temperatures the polymeric dispersion of poloxamer remains a solution at lower temperatures and becomes

API load thermosensitive in-situ nasal gel will be prepare by cold method.

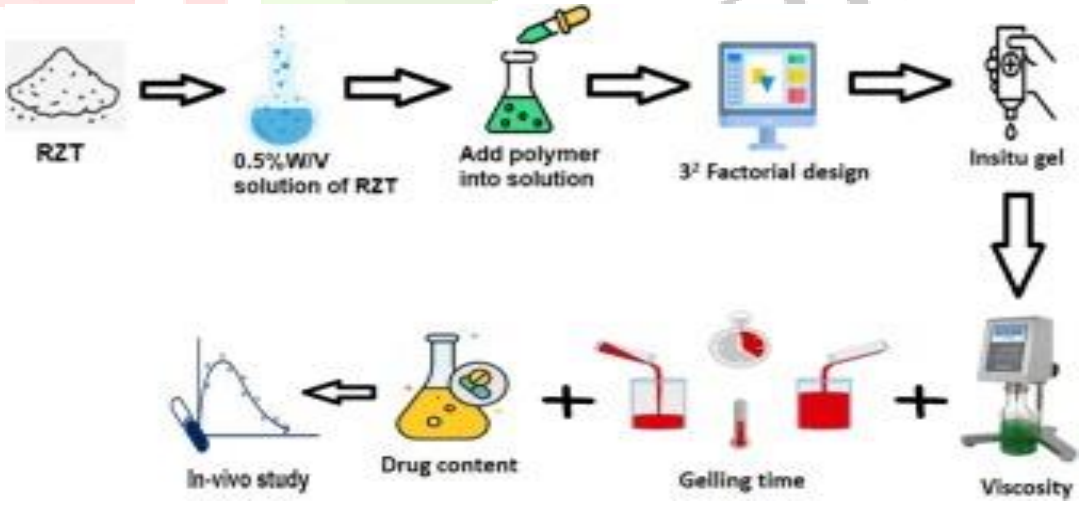
Poloxamer and carbopol will be dissolve in cold distilled water and kept at overnight for complete dissolution.

API will be dissolve in polyethylene glycol 400 and then add to the polymer solution while stirring continuously at low temperature.

Triethanolamine will be use to adjust the pH to approximately 6.4 to match nasal pH. The resulting formulation will be refrigerated to maintain stability until further use.

Hot Method:-

When using pectin or gellan gum as a gelling polymer, this method is recommended. Higher temperatures cause gellan chains to dissolve in water, assume a random coil shape with great segmental mobility, and continue as a solution above those temperatures. When gellan gum solution is cooled, sol-gel transition takes place in the presence of ions like K+ or Ca2+. Likewise, pectin requires a greater temperature for demethoxylation purposes which helps to formulate a solution or dissolve pectin. [23]



Method of Prepare of In Situ Nasal Gel

IN SITU GELLING FORMATION TRIGGERED:

In situ gel activated by temperature:

Certain polymers react to minor external changes in their ambient circumstances by undergoing significant and unanticipated physical and chemical changes. We refer to these polymers as stimuli-responsive polymers. Other names for them include intelligent, clever, stimuli-sensitive, and environmentally sensitive polymers. These polymers interpret a stimulus as a signal, determine the signal's strength, and adjust their chain conformation accordingly.the most researched class of environmentally responsive polymer systems in drug delivery is temperature-sensitive polymers. This is due to the fact that temperature can be readily controlled and applied both in vitro and in vivo. In this method, a change in temperature causes the fluid to gel, maintaining the drug release.at room temperature (20 to 25°c), these hydrogels are liquid, and when they come into contact with bodily fluids (35 to 37°c), they gel. An appealing method of approaching in situ formation is the use of biomaterials whose transition from sol-gel is induced by an increase in temperature. Ambient and physiological temperatures are the ideal critical temperature range for these systems, allowing for therapeutic manipulation and eliminating the need for an external heat source beyond the body's own to initiate gelation.

pH-triggered mechanisms

In-situ gel is also made by adjusting the gel's pH in response to physiological stimuli; in this case, pH-sensitive polymers were employed. The swelling of hydro gel increases when the external pH rises if the polymer contains weakly acidic groups, whereas it falls if the polymer contains weakly basic groups.

Types of thermoresponsive sol-gel polymeric system	**Properties of gel System**	**Common Polymers**
Negatively Thermosensitive	Have a lower critical solution temperature [LCST] and contract upon heating above the LCST.	Poly[Nisopropylacrylamide] [pnipaam]
Positively Thermosensitive	Has an upper critical solution Temperature [UCST]; such a hydrogel contracts upon cooling below the UCST.	Poly[acrylic acid][PAA] and polyacrylamide [paam]
Thermally Reversible	Polymer solution is a free flowing liquid at ambient temperature and Gels at body temperature.	Poly [ethylene oxide]-b-poly [propylene oxide]-b-poly[ethylene oxide] Pluronics®, Tetronics®, Poloxamers.

Chemically induced in situ gel system

Cross-linking of ions

Certain ions that are sensitive to polysaccharides, such as sodium alginate,carrageenan, gellan gum, and pectin, undergo activity transitions when various ions, including K+, Ca2+, Mg2+, and Na+, are present.These polysaccharides are with in the ion-sensitive group.

Cross-linking by enzymes On-site[3]

Although natural enzyme-catalyzed formation has not been widely studied, it seems to provide certain advantages over chemical and photochemical methods. For example, an enzyme The process works quickly under physiological settings without the need for potentially hazardous chemicals like initiators and monomers.

The process of photopolymerization :-For more than ten years, in situ photo-polymerization has been employed in biological applications. Gel can be created by injecting a solution of monomers or reactive macromers and initiator into a tissue location and applying electromagnetic radiation. Since they undergo photopolymerization quickly when an appropriate photoinitiator is present, acrylate or similar polymerisable functional groups are commonly utilised as the polymerisable groups on individual monomers and macromers. With the use of fibre optic cables, photopolymerizable systems that are injected into the targeted location undergo in situ photocuring, releasing the medication for an extended duration.

Factors Affecting Nasal Drug Absorption: Factors Influencing Absorption Are Related To Nasal Physiology, Physicochemical Characteristics Of Drugs And Formulation Aspects.

- Biological factors:

• Structural Features

• Biochemical Changes

• Physiological Factors

• Blood Flow

• Nasal Secretions

• pH Of The Nasal Cavity

•Mucociliary Clearance And Ciliary Beat Frequency Pathological Conditions

• Environmental Factors

• Temperature, Humidity.

I.physicochemical properties of drugs:

• Molecular Weight

• Size

• Solubility

• Lipophilicity

• Pka and Partition Coefficient

II.physicochemical properties of formulation:

• Dosage Form

• Viscosity

• pH And Mucosal Irritancy

III. device related factors:

• Particle Size Of The Droplet/Powder

• Size And Pattern Of Disposion

Biological factors:-

Biological factors have been identified in literature as significant influences.First and foremost, physiological factors encompass mucociliary function.Clearance is a significant factor contributing to this situation.The drugs are cleared from the nasal cavity.It entails the coordinated effort of the mucus layer and cilia at their tips.Cilia come into contact with the surface and assist in transportation.The viscoelastic mucus layer moves gently towards the nasopharynx.The lower layer of mucus with lower viscosity tends to be fairly still.Furthermore, a wide variety of metabolic enzymes are available.Within the lining of the nose. This may restrict the bioavailability of.Drugs administered nasally, on the other hand, can impact the level of activity.The level of these enzymes is lower compared to those found in the gastrointestinal tract.As well as the liver. Additionally, health issues such as rhinitis.The common cold may also impact the absorption of medications.The nasal cavity, as well as the ph level within it, can also have an impact.The penetration of medication. A shift in the ph levels of mucus may lead to changes.Influence the ionization process, leading to either an increase or decrease in the outcome.The penetration of the drug is influenced by the characteristics of the drug.

The physicochemical properties:- of drugs are explored in section 23.Different physical and chemical properties of a drug can also influence its absorption through the nasal route.

Molecular Weight and Size:- [9,1,4]

The absorption of a drug is greatly influenced by its molecular weight, especially when dealing with hydrophilic compounds. The nasal route is ideal for effectively administering drugs weighing up to 1000 Daltons. Absorption is notably decreased when the molecular weight exceeds 1000 Daltons, unless penetration enhancers are utilized. A strong linear correlation has been noted linking the log percentage of drug absorption through the nose to the log molecular weight of water-soluble compounds. This indicates the likely involvement of aqueous channels in the nasal absorption process of water-soluble molecules. It has been noted that particles larger than 10 μm tend to settle in the nasal cavity. Particles ranging from 2 to 10 μm have the ability to be trapped in the lungs, while particles smaller than 1 μm are typically breathed out.

Solubility and Dissolution:-

The physicochemical properties of drugs are explored in section 23.Different physical and chemical properties of a drug can also influence its absorption through the nasal route.Weight and dimensions at a molecular level.The absorption of a drug is greatly influenced by its molecular weight, especially when dealing with hydrophilic compounds. The nasal route is ideal for effectively administering drugs weighing up to 1000 Daltons. Absorption is notably decreased when the molecular weight exceeds 1000 Daltons, unless penetration enhancers are utilized. A strong linear correlation has been noted linking the log percentage of drug absorption through the nose to the log molecular weight of water-soluble compounds. This indicates the likely involvement of aqueous channels in the nasal absorption process of water-soluble molecules. It has been noted that particles larger than

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Chemical form :-

The presentation of a drug in a specific chemical form at the nasal mucosa can play a crucial role in its absorption process. For instance, altering a drug into a salt or ester form can affect how it is absorbed by the body. This occurrence is linked to the rise in lipophilicity that occurs after esterification, resulting in an increased speed and amount of nasal absorption.

Partition coefficient and pka :-

this are being considered.the relationship between the partition coefficient and nasal absorption remains constant in a quantitative manner. According to the ph partition theory, the absorption of unionized species is more efficient than that of ionized species, which also applies to nasal absorption. Absorption levels are influenced by the ph, with a higher rate observed at ph levels below the pka, decreasing thereafter. Generally speaking, the authors discovered that the absorption through the nasal passage increases in tandem with the permeant's lipophilicity. Numerous studies suggest that drug levels in the cerebrospinal fluid (csf) tend to elevate as the drugs' lipophilicity or partition coefficient increases.

Physical form of formulation:-the absorption of drugs through the nasal passage is influenced by the specific physical characteristics of the formulation being administered. Viscosity of the formulation stands out as a crucial parameter in formulation development. Typically, a thicker formulation tends to result in a lower efficacy in delivering drugs through the nasal system. The inclusion of viscous agents in nasal desmopressin delivery can lead to a slightly longer-lasting impact. It would be reasonable to assume that thicker formulations, for example. Gels would be a more suitable option for drugs that have a localized effect.

Ph of Formulation:-

The ph of the method as well as that of nasal floor can have an effect on a drug’s permeation. The ph of the nasal system is critical for the subsequent reasons,

- To keep away from inflammation of the nasal mucosa.
- To permit the drug to be available in unionized shape for absorption.
- To prevent the increase of pathogenic micro organism inside the nasal passage.
- To maintain functionality of excipients along with preservatives.

To sustain normal physiological ciliary movement. Lysozymes are found in nasal secretions which are responsible for destroying certain bacteria at acidic ph. Under alkaline conditions lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a ph of 4.5 to 6.5.

Buffer capacity:-

Solution to resist changes in ph is known as buffer capacity.nasal formulations are typically given in small amounts, usually between 25 and 200µl, with 100µl being the most frequently used dose volume. Therefore, nasal secretions can change the ph of the given dose. This can influence the amount of uncharged drug that is able to be absorbed. Hence, it may be necessary to have an appropriate buffer capacity in the formulation for ph maintenance.

Osmolarity:-

The absorption of drugs may be influenced by the tonicity of the formulation. The epithelial cells have been observed to shrink when exposed to hypertonic solutions. The hypertonic saline solution can also hinder or halt ciliary activity. A low ph has an effect comparable to that of hypertonic solutions. Typically, an isotonic solution is the preferred choice.

Gelling/viscofying agents or gel forming carriers:-

Certain formulations must be thickened or made more viscous in order to enhance their residence time in the nasal cavity. Elevating the viscosity of the solution could potentially extend the therapeutic impact of nasal products. The utilization of a drug carrier like hydroxypropylcellulose showed effectiveness in enhancing the absorption of low molecular weight drugs, however, it did not yield the same results for high molecular weight peptides. It's often advised to use a mix of carriers for safety reasons, specifically in relation to nasal irritancy.

Solubilizers:-

The solubility of a drug in water presents a consistent challenge for delivering drugs nasally in liquid form. Traditional solvents or co-solvents, including glycols, small amounts of alcohol, transcutol, medium chain glycerides, and labrasol, may be utilized to improve the solubility of medications. Additional alternatives include utilizing surfactants or cyclodextrins like hp-β-cyclodextrins, which act as a biocompatible solubilizer and stabilizer alongside lipophilic absorption enhancers. In such instances, it is important to take into account their effects on nasal irritation.

Preservatives:-

Typically, nasal formulations are water-based and require preservatives to inhibit the growth of microorganisms. Common preservatives found in nasal formulations include parabens, benzalkonium chloride, phenyl ethyl alcohol, edta, and benzyl alcohol.

Antioxidants:-

Antioxidants might need to be incorporated in a chosen drug formulation to safeguard against potential drug degradation, based on the stability characteristics of the drug. Frequently employed antioxidants include sodium metabisulfite, sodium bisulfite, butylatedhydroxytoluene, and tocopherol.

Humectants:-

Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel based nasal products to avoid nasal irritation and are not likely to affect drug absorption some common humectants used encompass glycerin, sorbitol and mannitol.

Absorption enhancers:-

In cases where a nasal product struggles to achieve its desired absorption profile, it is advisable to consider incorporating absorption enhancers. The choice of absorption enhancers relies on their approval by regulatory bodies and their effects on the nose's physiological processes. Absorption enhancers could potentially be necessary in cases where a drug faces challenges with membrane permeability, has a sizable molecular structure, lacks lipophilicity, or is susceptible to enzymatic degradation. After pinpointing a suitable enhancer, it is essential to experimentally establish its ideal concentration. Increased amounts of enhancers typically lead to nasal irritation and harm to the nasal lining. Conversely, using lower concentrations of enhancers would typically result in minimal to no enhancement in absorption.

➢ Evaluation Parameters of Nasal In-Situ Gels

Sr.no	Therapeutic molecules	Category	Polymer	Inferences	References
1	Artemether (Containing hydroxy propyl B-cyclodextrin) inclusion complex	Antimalarial	Pluronic, HPMC K4M	Showed good mucoadhesion strength and good stability at accelerated conditions over a period of 90 days.	Iguchi et al. (2014)
2	Curcumin	Anti inflammatory	Capryol 90, Solutol HS 15, Transcutol HP	Compared to the IV route, the nasal route is better for direct drug transport to brain	Wang et al. (2012)
3	Metoclopramide HCL	Antiemetic	Gellan gum, Xanthan gum	Sustained release of drug, improved drug absorption.	Kasirer et al. (2014)
4	Metoprolol Succinate	Antihypertensive	Pluronic F127, Sodium alginate	Bioavailability improved, avoid first pass effect.	Whayne (2014)
5	Midazolam HCL	Anticonvulsant	Ficus carica mucilage(0.5%,0.1%&1.5%) synthetic polymers (HPMC and Carbopol 934)	Higher bioavailability, higher permeation through Ficus carica mucilage rather than synthetic polymers	Basu and Bandyopadhyay (2010)
6	Ondansetron Hydrochloride	Antiemetic	PF 127 as thermosensitive HPMC as	Increase in bioadhesive strength, diffusion-controlled release of drug.	Singh et al. (2013)
7	Ondansetron Hydrochloride	Cancer chemotherapy	Pluronics 127 P, HPMC	Diffusion-controlled Release	Chen et al. (2010)
8	Radix Bupleuri	Antipyretic	20% Poloxamer as gel base 6% PEG 4000	Longer residence and release time.	Chen et al. (2010)
9	Sumatriptan Succinate	Antimigraine	Pluronic F127, Carbopol 974	Controlled drug release with higher permeability rate by using permeation enhancer, fulvic acid.	Zhao et al. (2014)
10	Zolmitriptan	Antimigraine	Sterculia foetida gum	Improved bioadhesion, increased permeation, and increased bioavailability of drug.	Bird et al. (2014)

• Clarity:

The black and white backdrop allows for visual assessment to verify the clarity.

• Texture analysis:

To make the preparations easier to deliver in vivo, a texture analyser may be used to assess the formulation's cohesion, stiffness, and homogeneity as key indicators of the sol's syringe capacity.

• Viscosity:

Various viscometers, such as the Brookfield viscometer, cone, and plate viscometer, can be used to measure the viscosity and rheological characteristics of the polymeric formulations, either in solution or in gel made with artificial tissue fluid. The viscosity of these formulations should be such that it should be patient compliance.

• Drug Content

A 10 ml volumetric flask was filled with 1 ml of the formulation.

The produced solution's absorbance was then measured using a U.V. visible spectrophotometer at a specific drug wavelength after it had been diluted with 10 ml of distilled water, the volume was adjusted to 10 ml, and 1 ml of this solution was once again diluted with distilled water up to 10 ml.

• Gel strength

A rheometer can be used to assess this parameter. A certain volume of gel is made in a beaker from the sol form, depending on the gelling agent's process. Pushing a probe gently into the gel is necessary because the beaker containing the gel is lifted at a specific rate. The probe's depth of immersion beneath the gel surface can be used to assess variations in the load on the probe.

• Gelling Temperature

The thermosensitive in situ gel is the focus of this test. After transferring the 2 ml in situ gel to a test tube and submerging it in a water bath, the water bath's temperature grew steadily and gradually. After five minutes of gel equilibration at each setting, the formulation was checked for gelation. A gelation temperature is reached when the meniscus would no longer move when tilted to a 90° angle.

• Sol-gel transition temperature and gelling time:

For in situ gel forming systems, it is necessary to measure the sol-gel process's ph and temperature. The amount of time needed to initially identify in situ gelling is known as the gelling time. It is necessary to evaluate the thermosensitive in situ gel for in situ gelling at body temperature.

• Drug-polymer interactions and thermal analysis:

Fourier Transform Infrared (FTIR) Spectroscopy can be used to determine the results of an interaction study. The nature of the interacting forces may be assessed by using the kbr pellet method. The proportion of water in hydro gel may be determined using the thermogravimetric Analysis (TGA) for in situ formation technique. When compared to the pure active substances used for gelation, the Differential Scanning Calorimeter (DSC) is utilised to identify any differences in thermogram.

• Gelling capacity:[6,7,8,9]

To determine the gelling capability of an ophthalmic product, mix in-situ gel with simulated tear fluid in a 25:7 ratio, meaning that the application volume is 25 µl and the volume of tear fluid in the eye is 7 µl. By recording the amount of time it takes for the gel to dissolve, the gelation may be visually evaluated.

• Sterility Testing [6,7,9]

Testing for sterility is done in accordance with IP 1996 For at least 14 days, incubate the formulation in the fluid thioglycolate medium at 300˚–350˚C to detect bacterial growth, and in the soyabean casein digest medium at 200˚–250˚C to detect fungal growth.

• Accelerated stability studie:[6,7,8]

According to ICH state criteria, the formulation is refilled in amber-colored vials and sealed with aluminium foil for short-term accelerated stability at 40˚±20˚C and 75±5% RH.

• In vitro drug release study

The plastic dialysis cell is used to perform in situ preparations for the nasal, ocular, and drug release tests. The cell is made up of two half cells, one for the donor and one for the receptor. Cellulose membranes are used to separate these. The donor container is filled with the prepared sol form. The completed cell is then shaken horizontally in an incubator. At regular intervals, the whole volume of the receiver solution may be taken out and swapped out for new media. Analytical receptor media are used to analyse this receptor solution, which is then put in a shaker water bath with the proper temperature and oscillation rate. Samples are frequently taken out and looked at.

Conclusion

The present article is focus on the studying all the parameters/element of in-situ gelling system. Traditional and conventional medication delivery methods have a number of issues and drawbacks, some of which reduce their effectiveness and, consequently, their appeal. Nasal in situ gel drug delivery devices have gained increasing attention in this context as a potentially successful and efficient drug administration technique. After nasal injection, these systems exhibit a phase change from a sol to a gel state. This improves the medicine's bioavailability and therapeutic efficacy by facilitating sustained drug release and extending its duration in the nasal cavity. They offer a patient-friendly, non-invasive approach to medicine delivery since, unlike invasive methods, they don't require specific training for administration, making it a sensible choice for patients, particularly those who cannot withstand intrusive medical procedures. This patient-friendliness and non-invasiveness may improve therapeutic outcomes by increasing patient compliance and adherence.

another advantage of nasal in situ gel medication delivery systems is their ability to cross the blood-brain barrier and directly target the central nervous system. Drugs can swiftly and directly enter the brain through the nasal cavity's olfactory region thanks to this capability. Because of this, they may be a desirable substitute for treating disorders of the central nervous system. Additionally, medications' absorption and therapeutic effectiveness can be enhanced. The formulations can gel when they come into touch with the nasal mucosa, prolonging the drug's residence duration in the nasal cavity and facilitating greater absorption and longer release. Consequently, the

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