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A Review on Nasal in-Situ Gel

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A B S T R A C T

The most preferred method for delivering the medication orally into the body is the oral route. Due to various restrictions such drug absorption, low bioavailability, and first-pass hepatic metabolism, drugs that target certain organs may pose issues when administered orally. Therefore, alternatives to the oral route include the maternal route, transmucosal route, and transdermal method. Because the temporal profile of drug concentration via the intranasal route is comparable to that of the intravenous route, it is seen to be a desirable approach. A novel medication administration method, the in-situ nasal drug delivery system, has been developed to improve patient safety and efficacy. Drugs are delivered as a low viscosity solution in in-situ nasal gels. When the polymer comes into touch with nasal mucosa, its structure changes to gel. The nasal gel formulation is ideal for medications whose oral administration is difficult due to gastrointestinal discomfort, drug absorption, low bioavailability, and first-pass hepatic metabolism. Various triggered polymers are employed in the gel formulation. The current study concentrated on therapeutic considerations, architecture and physiology of the nasal cavity, problems, and possibilities in nasal drug administration, commercialized in-situ nasal gel products, and numerous assessment factors evaluated during in-situ gel manufacture.

Keywords: In-situ,nasal-gel,polymer,bioavilability,dru

1.Introduction: -

When systemic effects are desired, oral medication delivery is the desirable, preferred, and practical method for drug administration due to its simplicity in manufacturing and administration. However, certain actives' limited oral bioavailability as a result of significant hepatic metabolism & gastrointestinal degradation has motivated researchers to look for more efficient ways to distribute them to the body. Parenteral, transdermal, and transmucosal modes of drug delivery—which target the mucosal inner lining of the sinus, rectal, vaginal, and buccal cavities—offer significant benefits over oral administration. For the local and systemic distribution of different medicinal substances, intranasal administration provides a practical option. Since the nasal mucosa has a wide surface area, it can carry drugs directly to the central nervous system, avoid first pass metabolism, and appear non-invasive, all of which may increase patient comfort and compliance. High molecular weight medicinal substances like proteins and peptides are prevented from entering the body by the nasal mucosa. It is possible to reversibly and safely open the tight connections that are obstructing paracellular medication transport. The patient can easily and quickly give intranasal therapy since it is non-invasive, painless, and does not require sterile preparations, such as in an emergency.[1]

These include the potential bypass of the first-pass effect and the avoidance of the need for a tiny dosage of a certain medicine. Lowering the dose will lessen the negative effects and, ultimately, lower the cost of the medication. While the parenteral route is connected to pain at the injection site, lower patient compliance, and inconvenience for long-term therapy, the transdermal route, on the other hand, is restricted in its use due to the poor permeability of the skin to several drugs, despite being effectively exploited for delivery of some drugs. Less popular methods include transmucosal, vaginal, and rectal since they irritate patients and have lower compliance rates. Drugs with a bad taste may have acceptance issues when taken orally. [1,2]

Additionally, intranasal administration offers a practical method for the transport of medications to the central nervous system (CNS) as well as to administer treatments with localized effects. From the perspective of the patient (rapid onset of action, non-invasiveness, essentially pain free, ease of delivery, favorable tolerability profile, enhanced patient compliance, easiness of convenience, self-medication), as well as the pharmaceutical industry, intranasal administration has a number of practical benefits (no need of sterilization of nasal preparations). Therefore, it appears to be a good route for such treatment of not only acute or chronic nose problems, but also for systemic effects, if the inherent value of the intranasal route can overcome patient compliance is enhanced with its pharmacokinetic benefits.[3]

Use of the peripheral and central nervous systems are both impacted by neurological illnesses. These comprise the muscles, neuromuscular junction, cranial nerves, spinal cord, brain, and peripheral nerves. Parkinson's disease, epilepsy, multiple sclerosis, Alzheimer's disease, cerebrovascular illnesses, brain tumors, etc. are a few examples of neurological diseases. Millions of individuals worldwide are affected by neurological illnesses. According to the WHO (World Health Organization), dementia affects 47.5 million people worldwide, and 7.7 million new cases are discovered each year. Alzheimer's

disease is the most prevalent kind of dementia, accounting for 70% of cases. Neurological disorders can be caused by a variety of reasons, including genetics, physical harm, infections, ageing, lifestyle, diet, and environmental variables. The delivery of treatments topically, orally, intravenously, the use of device-based therapies such deep brain stimulation, surgeries, and rehabilitation are all used in the treatment of neurological illnesses. Some methods involve administering the medication directly into the brain, cerebrospinal fluid, or nasal cavity. Some of these methods are risky, intrusive, localized, and transient. The repair of the central nervous system, which entails the regeneration of the injured neural tissue, is another method for treating neurological illnesses. However, neurodegeneration limits this strategy. Additionally, the blood-brain barrier serves as a barrier that prevents some therapeutic compounds from reaching the brain's endothelial capillaries and some therapeutic agents from reaching the central nervous system. [1,2]

2.Nasal route drug absorption mechanism:

The mucus layer and epithelium membrane are crossed by medications that have systemic or CNS effects in order to reach the blood circulation or the CNS itself, respectively. Drug absorption is thought to occur in the respiratory area, which includes the turbinates and a portion of the nasal septum, for the systemic impact. The most important place from which a medication may be absorbed directly into the brain for CNS effects is the olfactory area, which is close to the respiratory region. When a medication is administered intravenously, it can either travel directly from the olfactory area to the brain, via the blood (systemic circulation), or via the trigeminal neural pathway, which allows the drug to partially travel from the nasal cavity to the cerebrospinal fluid (CSF).[4]

In order to target medication molecules working on the CNS in illnesses including Alzheimer's disease, Parkinson's disease, depression, migraine, schizophrenia, epilepsy, brain tumours, psychosis, and pain, the olfactory area of the nasal mucosa can be used as a direct link between the nose and the brain. Drugs must first travel through mucus in the nasal cavity in order to be absorbed. The mucus layer is easily penetrated by small, uncharged particles. Large or charged particles, however, could find it challenging to get through the mucus layer. The main protein in mucus, mucin, has the ability to adhere to solutes and obstruct the diffusion of medicines. There are a number of routes for medication absorption via the mucosa once it has passed through the mucus.[3]

2.1 Paracellular route:

The watery route of transport is another name for the paracellular pathway. The medication is transported through the epithelium via openings or pores between tight junctions via this passive, sluggish pathway. Tight junctions are dynamic, between-cell structures that can partially open and close. The size of these channels is less than 10 A0. In order to prevent the passage of big molecules, a molecular size cutoff of 1000 D is based on the drug's molecular weight. However, for medications with a molecular weight of at least 6000 D, excellent bioavailability can be increased with the use of permeation enhancers. Polar medications with low bioavailability when administered nasally include alniditan, morphine, sumatriptan, insulin, mannitol, calcitonin, and leuprolide. These medications are carried by the paracellular pathway.[2]

2.2 Tran cellular route:

Medications that are lipophilic are transported by a lipoidal pathway called the transcellular route, and this route exhibits a rate dependence on the lipophilicity of the drugs being transported. It involves effective receptor or carrier mediation, concentration-dependent passive diffusion across the cell's interior, and vesicular transport mechanisms. Organic cation transporters and amino acid transporters are examples of the carriers that facilitate transcellular transport in the nasal mucosa. It appears that endocytic mechanisms are responsible for the transcellular transport of substances having a molecular weight more than 1000 D, such as proteins and peptides. When administered nasally, lipophilic medications such as propranolol, progesterone, pentazocine, and fentanyl exhibit quick and effective absorption.[4]

2.3 In situ nasal gels provide the following benefits over other nasal formulations:

I. A decrease in post-nasal drip into the back of the throat, which minimizes the problem of foul taste and medication loss from the nasal cavity.
II. A reduction in the drug's anterior nasal cavity leaking.
III. Localization of the formulation on the mucosa, which increases the likelihood that the medication will be absorbed.
IV. Gels can use emollients or soothing ingredients that may not be appropriate for solutions, suspensions, or powder dosage forms, which can lessen the likelihood of irritation.
V. May be created for both systemic and local distribution, and
VI. A metered dosage nasal actuator system can be used to provide a precise dose.as shown in fig.1. [1,4,5]

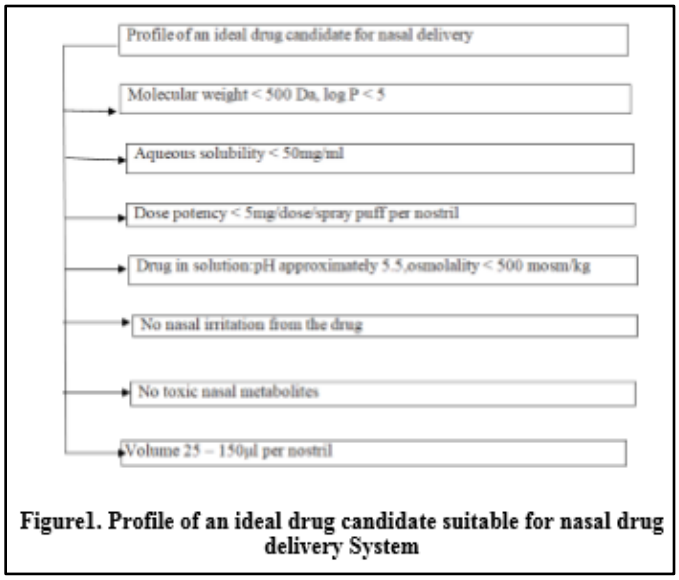

Figure1. Profile of an ideal drug candidate suitable for nasal drug delivery System

2.4Present-day methods for improving nasal permeation:[5,6,7]

The bioavailability of nasally given medicines is generally constrained due to low drug solubility, fast enzymatic degradation in the nasal cavity, weak membrane penetration, and quick mucociliary evacuation. There have been several approaches proposed to get around those restrictions: -

2.4.1 Prodrugs:

Lipophilic medications easily flow across bio membranes since they are not very water soluble. They should be provided as prodrugs with increased hydrophilic character in order to increase the likelihood of the creation of an aqueous nasal formulation with an acceptable concentration. When in the bloodstream, the prodrugs must be quickly transformed into the parent medication. For instance, several prodrugs of L-Dopa have better solubility than the parent drug, which has facilitated the development of effective nasal formulations.[6]

2.4.2 Co-solvents:

Using co-solvents is an alternate strategy for prodrugs to boost drug solubility. Glycerol, ethanol, propylene glycol, and polyethylene glycol are among the common co-solvents used in intranasal formulations, and they may be the most important since they are non-toxic, suitable for use in pharmaceutical formulations, and don't irritate the nasal mucosa [5].

2.4.3 Enzymatic inhibitors:

Because nasal mucosa contains a variety of enzymes, it acts as an enzymatic barrier during nasal medication delivery. To prevent enzymatic breakdown, a variety of techniques are utilized, including protease and peptidase inhibitors. As tyrosine inhibitors likely implicated, amino peptidases are utilized as inhibitors in the breakdown of substances including calcitonin bestatine, comostate amylase, leupeptin, and aprotinin. Furthermore, bacitracin, amastatin, boroleucin, and puromycin have been used to aid stop the enzymatic breakdown of medications such leucine encephalin. Finally, absorption enhancers like may also be used to perform the enzymatic decrease (bile salts and fluidic acid). The beta-sheet breaker peptide used to treat Alzheimer's disease has been found to prevent enzymatic degradation when administered with disodium EDTA, an absorption enhancer.[7]

2.4.4 Permeation Enhancer:

Small and big hydrophilic medicines may have inadequate nasal epithelial permeability and hence show limited bioavailability. Permeation enhancers. By delivering in tandem with absorption enhancers that alter the epithelial barrier structure in a reversible manner, the penetration can be enhanced.

3. IN-SITU NASAL GEL FORMULATION METHODS:

In general, two procedures are frequently employed to prepare in-situ nasal gel:

a) Cold method:

In this formulation procedure, the product and a sample amount of double-distilled water are combined in a refrigerator and stored overnight at 4°C. The in-situ gelling polymer is then gradually added again while being stirred continuously. The dispersion is kept in a refrigerator until a clear solution is designed and the volume is adjusted. This approach is chosen when formulations call for gelling polymers such poloxamer, chitosan, or carbopol. Because the solubility of the propylene oxide chain in poloxamer declines at high temperatures, causing precipitation or salting from polymer, the polymeric dispersion of poloxamer remains as a solution at lower temperatures and is concentrated in gel at higher nasal temperatures. Similarly, chitosan frequently needs low temperatures to remain a solution at room temperature, and as temperature rises, so does its hydrophobicity. [8,9]

b) Hot Method:

If pectin or gellan gum is employed as the gelling polymer, this method is favoured. At higher temperatures, gellan chains dissolve in water and assume a random coil confirmation with great segmental mobility. They also move forward as a solution. Gellan gum solution undergoes sol-gel transition

when chilled in the presence of ions like K+ or Ca2+. Similar to how pectin requires a greater temperature for demethoxylation in order to be dissolved or formed into a solution.[9]

- TRIGGered in the formation of Situ Gelling

1. In situ gel activated by temperature

There are some polymers that, in reaction to little external changes in their ambient circumstances, go through significant and unanticipated physical and chemical changes. Stimuli-responsive polymers are those that respond to stimuli. The terms stimuli-sensitive, intelligent, smart, or environmentally sensitive polymers are also used to describe them. These polymers distinguish between stimuli and signals, assess the strength of the signal, and modify their chain confirmation in response.

The most well researched class of environmentally responsive polymer systems for drug delivery is temperature sensitive polymers. This is because temperature can be readily controlled and applied in both in vitro and in vivo settings. A change in temperature in this system causes the fluid to gel, continuing the drug release. These hydrogels are liquid at room temperature (20–25 °C), and when they come into contact with bodily fluid (35–37 °C), they begin to gel. An appealing method of approaching in situ formation is the use of biomaterials whose transition from sol-gel is induced by rise in temperature. The ideal critical temperature range for such systems is ambient and physiological temperature, which allows for easy clinical manipulation and doesn't require any heat from sources other than the body to cause gelation.[10]

Polymers that change with temperature might be,

I. Positive thermosensitive gels: The system does have an upper critical solution temperature (UCST), and the hydrogel in question shrinks when the UCST is lowered. Polymer networks, for instance (acrylic acid) [10,11,12]
II. Negative thermosensitive gels: The system contracts when heated over its lower critical solution temperature (LCST). E.g., poly (N-isoprophylacrylamide)
III. Thermo reversible gels: such with tetronics and poloxamers/pluronics.

2. In situ gel induced by pH:

pH is another physiological stimulus that causes in situ gel to develop. When exposed to various ambient pH levels, the acidic or basic groups in the polymers that make up this class either receive or release protons. This is why they are known as pH sensitive polymers. The majority of anionic polymers that are pH-sensitive are based on PAA (Carbopol®, Carbomer) and its derivatives.

3. Ion-activated in situ gel:

This kind of gelation involves polymers that go through a phase change when there are ions present. When monovalent and divalent cations like Ca2+, Mg2+, K+, and Na+ are present in the nasal discharge, an anionic polysaccharide called gellan gum passes through a phase change.[12]

❖ **NASAL IN-SITU GELS EVALUATION PARAMETERS:**

I. Clarity: The clarity will be evaluated using a visual inspection against a black and white background.
II. Viscosity: Using a variety of viscometers, including the Brookfield viscometer, cone and plate viscometer, it is possible to determine the viscosity and rheological characteristics of the polymer formulation in a solution or gel generated from synthetic tissue fluid.
III. Texture analysis: To establish the formulation's hardness, homogeneity, and cohesiveness in order to make it easier to give the preparation in vivo, texture analysis may be used as one of the primary indicators of the syringe capacity of solution.
IV. Drug content: 1ml of the produced solution is placed in a 10ml volumetric flask, diluted with 10ml of distilled water, and then made up to 10ml. 1ml of this solution was diluted once more with distilled water up to a total of 10ml. Tests are conducted on prepared solutions at certain wavelengths using UV visible spectroscopy.
V. Gel strength: A rheometer may be used to assess gel strength. In a beaker, a certain amount of gel is made. The gel is punctured by a probe. The variation in load on the probe may be calculated as a function of how deeply it is buried beneath the gel surface.
VI. Sol-gel transition temperature and gelling time: For in-situ gel forming systems, the temperature and pH of the sol-gel process should be monitored. Gelling time is the amount of time needed to actually notice in-situ gelling. It is necessary to evaluate the thermosensitive in-situ gel for in-situ gelling at body temperature. [13,14]
VII. Study of drug-polymer interactions and thermal analysis:
Infrared Fourier transform (FTIR) spectroscopy can be used to analyses interactions. The approach of using KBr pellets allows for the measurement of the interacting forces' nature. The proportion of water in hydro gel may be determined using the thermo gravimetric analysis (TGA) for in-situ production technique. Using a differential scanning calorimeter (DSC), it is possible to measure thermogram differences from purified active substances utilized in gelation.
VIII. Gelling capacity: To determine the gelling capacity of an ophthalmic product, mix in-situ gel with simulated tear fluid (in the ratio of 25:7, i.e., application volume 25 l and volume of tear fluid in eye is 7 l). By observing the amount of time, it takes for the gel to develop and dissolve, one may visually evaluate the gelation process.
IX. Sterility testing: In accordance with IP 1996, sterility testing is done. For this test, incubate the formulation for 14 days at 300° to 350°C in a fluid thioglycolate medium to look for bacterial growth and at 200° to 250°C in a soybean casein digest media to look for fungal growth.[14]
X. Accelerated stability studies: When aluminum-sealed amber vials fail, the formulation is temporarily changed. According to ICH state norms, the accelerated stability was performed between 40°–20°C and 75–5 percent relative humidity.
XI. Invitro drug released study: In-situ preparations are administered by the nasal, ocular, and drug release assays are performed using a plastic dialysis cell. In vitro drug release research. A donor compartment and a receptor compartment are located in each of the two half cells that make up the cell. By means of cellulose membrane, they are separated. The donor container is filled with the prepared sol form. The completed

cell is then shaken horizontally in an incubator. At regular intervals, the receiver solution can be completely removed and replaced with new media. This receptor solution is put in a shaker water bath at the proper temperature and oscillation rate, then evaluated using analytical receptor media. Samples are often taken and looked at.

❖ **USE OF AN IN-SITUT MEDICATION DELIVERY SYSTEM:**

In-situ medication administration may take one of the following forms:

➢ Oral drug delivery system:

Pectin, xyloglucan, and gellan gum are examples of natural polymers that are employed to create in-situ oral drug delivery systems. Normally, calcium ions are needed to form the gels employed as drug delivery vehicles since pectin typically gels in the presence of H+ ions, a source of divalent ions. According to reports, paracetamol is an oral in-situ gelling pectin formulation for as long-lasting a delivery as feasible.[1,15]

➢ Ocular drug delivery system:

The most often utilised natural polymers for in-situ producing oral drug delivery systems are gellan gum, alginic acid, and xyloglucan. For this reason, the several substances including antimicrobials, anti-inflammatory medications, and autonomic pharmaceuticals that are primarily utilised to reduce intraocular stress in glaucoma have been employed for the local administration of ophthalmic drugs. The toxins are swiftly eliminated from the eyes because of the high tear production and complexity. The bioavailability and therapeutic outcomes of traditional administration methods are frequently inadequate. Therefore, issues with bioavailability in ocular in-situ gels have been discovered. Gellan's aqueous solution lowered into the eye undergoes a change to gel state due to the temperature and ionic content (Ca++) in the tear fluid. The use of gellan gum for ocular medication administration has garnered the most attention in the pharmaceutical industry. Because the viscous gels have longer precorneal contact periods than traditional eye drops, the medication release from these in-situ gels is delayed.[2,16]

➢ Nasal drug delivery system:

An in-situ gel delivery system for mometasone furoate was created, and its effectiveness and safety in treating allergic rhinitis were evaluated via the nasal route. As an in-situ gel forming mechanism, polymers like xanthan gum and gellan gum have been employed. The in-situ gel's effects on antigen-mediated nasal symptoms have been seen in sensitised rats in animal investigations that used an allergic rhinitis paradigm. In-situ gel was discovered to reduce the rise in nasal symptoms when compared to the commercial version of nasonex (mometasone furoate solution 0.05%).[17]

➢ Rectal drug delivery system:

It may also be used for rectal and vaginal medication administration in-situ gels. Miyazaki et al. investigated the use of xyloglucan-based thermoreversible gels for indomethacin rectal medication administration.

➢ Vaginal drug delivery system:

For the treatment of vaginitis, a mucoadhesive, thermosensitive, extended-release vaginal gel integrating clotrimazole—cyclodextrin complex was developed, which improves therapeutic efficacy and patient compliance. Pluronic F-127 was combined with mucoadhesive polymers such as Carbopol 934 and hydroxylpropyl methylcellulose as an in-situ gel forming polymer to provide a lengthy residence duration at the application site.[17]

➢ Injectable drug delivery system:

For tumour therapy, a new, thermosensitive in-situ gelling hydrogel was created. It consists of a chitosan solution containing medicines that have been neutralised with -glycerophosphate.

4.Conclusion:

As an alternative route for such administration of medications and biomolecules that are subject to enzymatic or acidic degradation, go through first-pass hepatic metabolism, are insufficiently absorbed in the GIT, or have unfavourably slow effects when taken orally, nasal drug delivery is a rapidly developing field. The nasal route avoids the bioavailability problems brought on by the aforementioned considerations and has the benefit of regulated medication administration for prolonged periods of time. Patient compliance, which in situ gels may provide, is closely related to the success of such a controlled release solution. Utilizing polymeric in situ nasal gels enabling controlled medication release has several benefits over traditional dosage forms and is a dependable, non-invasive method of drug administration. Exploration of innovative gel triggering mechanisms, as well as the use of water-soluble, biodegradable polymers for product development of in situ nasal gel formulations, improves their acceptability.

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