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A Review on In-Situ Nasal Gel

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ABSTRACT

In situ gelling drug delivery techniques have garnered a lot of interest in the last ten years. When exposed to a range of endogenous stimuli, such as temperature increases, pH shifts, and the presence of ions, they can gel from their sol-state prior to injection. Systems can be given in a number of ways to facilitate the injection of a local or systemic treatment. They can also be used as efficient carriers for drug-carrying nanoparticles and microparticles. either natural, synthetic, or combined with a semi-artificial polymer that exhibits in situ gelling activity. In order to extend the time spent at the site of action or absorption, coupling with mucoadhesive polymers is greatly desired for the development of such systems. Because of the nasal epithelium's high permeability, quick drug absorption, avoidance of hepatic first pass metabolism, increased medicine bioavailability, and less side effects, nasal drug administration is a better option than oral and parental routes. undesirable local and systemic effects, self-medication, direct administration to the central nervous system and systemic circulation, low dosage requirements, and improved patient compliance. It is possible to stop stomach ulcers from developing. Many drugs have higher oral bioavailability than nasal bioavailability, according to recent data. Therefore, nasal medications are the main topic of this review.

Keywords: Bioavailability, In Situ Gel, Systemic Delivery, Nasal Drug Delivery System.

INTRODUCTION

One of the best methods for administering drugs is orally [01]. The oral bioavailability of certain drugs has encouraged the search for a more efficient systemic delivery pathway where systemic effects are planned [02].

Nasal mucosa is the main route of administration for transmucosal drug delivery, which aims to achieve a higher and faster amount of drug absorption [03]. One particularly promising delivery method has been transmucosal nasal administration.[04] It has been demonstrated that many medications have greater systemic absorption when taken via the nasal route as opposed to the oral route [05].

Due to its ease of usage, the oral route is the most preferred and practical way to administer drugs. However, when the medication degrades significantly in the liver due to a first-pass action, oral administration is frequently not recommended [06]. The process of creating a new medicinal molecule is costly and time-consuming [07].

Therefore, giving "old" medications in a targeted or controlled manner can increase their safety and efficacy ratio. As a result, in

situ gelling nasal medication delivery systems are created. Nasal drug delivery has its roots in the topical administration of medications meant to produce local effects. The Ayurvedic system of Indian medicine recognises nasal therapy, also known as "Nasya karma," as a kind of treatment [08]. When it comes to systemic administration, the nasal mucosa—the mucosal lining of the nasal, rectal, vaginal, ocular, and oral cavities—is the primary route of administration for achieving a higher and faster amount of drug absorption [09].

It has been acknowledged that nasal drug delivery is a very promising method of delivering medicinal substances. Many medications have demonstrated improved systemic bioavailability via the nasal route in recent years. This is because of the nasal route's wide surface area, porous endothelium membrane, high total blood flow, avoidance of first-pass metabolism, and easy accessibility [11].

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which has a conventional airway epithelium with numerous microvilli, offers a sizable area that is accessible for drug absorption and transportation **[16]**.

In this manner, the mucus layer is moved from the nasal cavity's anterior to its rarer region. The nasal turbinate and the atrium are shielded by the mucous membrane. Mucus granules, which are secreted by the goblet cells, swell in the nasal fluid and add to the mucus layer [17]. About 95% of the mucus secretion is made up of water, 2% mucin, 1% salts, 1% lipids, and 1% other proteins such albumin, immunoglobulin, lysozyme, and lactoferrin. The immunological response to inhaled germs and viruses is suppressed by the mucous discharge **[18]**.

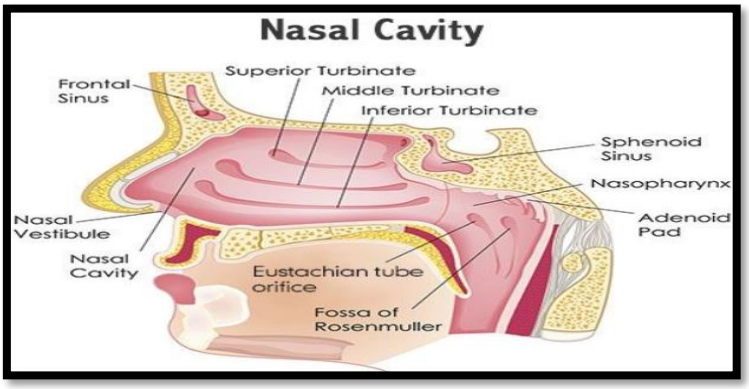

Fig no 01- Anatomy of Nasal cavity.

In Situ Formation Based on Physical Mechanism

Swelling-

In situ formation may also take place when material absorbs water from the surrounding environment and expands to occupy the desired space[19]. One such substance is myverol glycerol mono-oleate, a polar lipid that swells in water to form lyotropic liquid crystalline phase structures. This material exhibits bioadhesive properties and is capable of being degraded in vivo through enzymatic action [20].

Diffusion-

This approach entails the diffusion of solvent from the polymer solution into the adjacent tissue, leading to the precipitation or solidification of the polymer matrix. N-methyl pyrrolidone (NMP) has demonstrated its effectiveness as a solvent for this system [21].

Drug Absorption via Nasal Route

Mechanism-

The mucus layer must be penetrated for the medications to be absorbed from the nasal cavity. The process is currently in its initial phase of assimilation. Large, charged medications encounter difficulties in penetrating this barrier, whereas small, unaltered molecules can do so with ease [22]. Mucin serves as the primary protein component in mucus. The tendency to bind with solutes inhibits diffusion. Additionally, environmental factors may cause changes in the structure of the mucus layer [23].

In Situ Gel Formation Based on Physiological Stimuli

Temperature Induced In Situ Gel Systems

Temperature serves as the most commonly utilised stimulus in environmentally responsive polymer systems. The alteration of temperature is not only relatively straightforward to manage, but also readily applicable in both in vitro and in vivo settings. The gelling of the solution in this system is initiated by a change in temperature, thereby facilitating the sustained release of the drug[24]. These hydrogels remain in a liquid state at room temperature (20–25 °C) and transition to a gel form upon contact with body fluids (35–37 °C). As a result of a rise in temperature [25].

MATERIALS & METHODS

CHALLENGES AND OPPORTUNITIES FOR NASAL DELIVERY SYSTEMS-

The incentives for nasal delivery are unable to fully leverage the existing nasal delivery systems, including sprays, pumps, and pipettes. A significant portion of the dose is deposited on the frontal section associated with the skin, and the deposited drug is not intended for either topical application or systemic circulation [26]. The acceptance of patients has diminished due to the unpleasant taste and discomfort associated with medications administered via the nasal route. Ultimately, the challenge of extending nasal administration of drugs and vaccines is insufficient due to the intricate deposition in the distant areas associated with sinus and middle ear openings, as well as in the olfactory region. New advanced and expensive medications necessitate consistent bioavailability and a rigorous combination of reliable dosing and high patient adherence to validate their efficacy and safety. Liquid nasal products are primarily administered using metered spray pumps [27].

CURRENT APPROACHES FOR NASAL PERMEATION ENHANCEMENT-

The bioavailability of drugs administered nasally is significantly constrained due to factors such as low drug solubility, rapid enzymatic degradation within the nasal cavity, poor membrane permeation, and swift mucociliary clearance [28]. A variety of approaches to address those limitations have been proposed. The following methods are outlined and detailed below [29].

Prodrugs-

Lipophilic medications exhibit low solubility in water, allowing them to readily traverse biological membranes. To facilitate the development of an aqueous nasal formulation with an acceptable concentration, they should be delivered as prodrugs exhibiting enhanced hydrophilicity. The prodrugs must be swiftly converted to the parent medication upon entering the bloodstream. In contrast to the parent drug, numerous prodrugs of L-Dopa have enhanced solubility, hence facilitating the development of suitable nasal formulations [30].

Co-solvents-

To enhance drug solubility, the utilisation of cosolvents presents a viable alternative for prodrugs. The cosolvents commonly utilised in intranasal formulations comprise glycerol, ethanol, propylene glycol, and polyethylene glycol [31]. These substances are particularly significant due to their non-toxic nature, pharmaceutical safety, and non-irritating properties concerning nasal mucosa [32].

Enzymatic inhibitors-

The nasal mucosa layer functions as an enzymatic barrier in nasal drug delivery due to its diverse array of enzymes. Various methods are employed, including protease and peptidase inhibitors, to prevent enzymatic degradation. Amino peptidases serve as inhibitors in the degradation of calcitonin bestatine, while comostate amylase, leupeptin, and aprotinin act as tyrosine inhibitors that are likely involved in this process [33]. Additionally, to mitigate enzymatic degradation of drugs such as leucine enkephalin, bacitracin, amastatin, boroleucin, and puromycin, specific measures have been implemented. The enzymatic reduction can also be achieved through the use of absorption enhancers such as bile salts and fluidic acid. Disodium EDTA, recognised for its role as an absorption enhancer, has demonstrated efficacy in limiting the enzymatic degradation of beta-sheet breaker peptides utilised in the treatment of Alzheimer's disease [34].

Permeation enhancers-

Hydrophilic drugs, regardless of their size, can demonstrate inadequate permeability through the nasal epithelium, potentially leading to insufficient bioavailability [35]. The permeation can be enhanced by administering in conjunction with absorption enhancers that induce reversible alterations to the epithelial barrier structure[36].

Table no 01- Delivery System Based Approaches for Intranasal Drug Delivery

Formulation	Advantages	Disadvantages
Nasal spray [30]	Nasal sprays may be formulated in the form of solution and suspension. Exact dose can be delivered via metered dose pumps and actuators	Less efficient than nasal drops when human serum albumin is stored in the nostrils
Nasal drops [31]	Simple and convenient system	Lack of dose precision
Nasal gels [32]	Due to high viscosity reduction of post nasal drip, reducing the effect of tastes due to reduced swallowing and reduction of anterior formulate leakage	Local side effects
Nasal powders [33]	Absence of preservatives and superior stability.	The appropriateness of powder composition depends on the solubility, particle size, aerodynamic properties and nasal discomfort of active drugs
Liposomes [34]	Active encapsulation of large and small molecules with high hydrophilicity and pKa values	Production cost is high Short half-life
Nanoparticles [35]	Deposits their small size	Only the smallest nanoparticles penetrate to the mucous membrane by paracellular route and in a limited amount

METHODS OF FORMULATION OF IN SITU NASAL GEL-

Cold method-

The formulation process involves mixing the product with a specified quantity of double distilled water, which is then stored in a refrigerator at 4 ºC overnight. Subsequently, the in situ gelling polymer is incorporated gradually while maintaining constant stirring [32].

The dispersion is stored in a refrigerator until a clear solution is formulated and volumes are adjusted accordingly. The selection of this method is appropriate when utilising gelling polymers such as poloxamer, chitosan, or Carbopol for formulation purposes. The polymeric dispersion of poloxamer remains a solution at lower temperatures and transitions to a gel at elevated nasal temperatures [33]. This behaviour is attributed to the decreased solubility of the propylene oxide chain of poloxamer at higher temperatures, leading to precipitation or salting out of the polymer.

Similarly, chitosan typically necessitates low temperatures to remain stable as a solution at room temperature, with its hydrophobicity escalating at elevated temperatures [34].

Hot Method-

This form is recommended when utilizing gellan gum or pectin as a gelling polymer [35]. Gellan chains exhibit solubility in water at elevated temperatures, adopting a random coil conformation characterized by significant segmental mobility under these conditions, thereby functioning as a solution at higher temperatures[36]. When ions such as K+ or Ca2+ are present, sol-gel transformation takes place as the gellan gum solution cools [37]. In a similar manner, pectin requires elevated temperatures for the purpose of demethoxylation, which facilitates the formulation of a solution or the dissolution of pectin [38].

Table no 02- SomeoftheexcipientsandAPIsusedinnasal*insitu*geldrugdelivery systems

API	Excipients
Sumatriptan [35]	Poloxamer 407, Carbopol 934P
Voriconazole [36]	Deacetylated gellan gum, Clove oil, Soybean lecithin, Tween 80
Almotriptan[37]	Poloxamer 407, Poloxamer 188
Metoclopramide [40]	Poloxamer 407, Polyethylene glycol, Hydroxypropyl cellulose, Carbopol 934P, Chitosan, Polyvinyl alcohol
Midazolam [38]	Gellan gum, Carbopol 934P
Levodopa [39]	Poloxamer 407, Chitosan
Budesonide [40]	Poloxamer 407, Propylene glycol
Lorazepam [34]	Gellan gum, Carbopol 934P

EVALUATION OF NASAL *IN SITU* GELS-

Clarity-

The visual inspection under a black and white backdrop will assess the clarity [35].

Viscosity-

The viscosity and rheological properties of the polymer formulation can be determined in solution or gel using artificial tissue fluid and various viscometers, including the Brookfield viscometer and cone and plate viscometer [36].

Texture analysis-

The primary indications of the syringe capacity of the solution can be assessed through the firmness, uniformity, and cohesiveness of the formulation using a texture analyser, ensuring that the preparations can be administered in-vivo with ease [37].

Drug content-

Approximately 1 ml of the prepared solution is transferred to a 10 ml volumetric flask, which is then filled to the 10 ml mark and subsequently diluted with 10 ml of distilled water. Approximately 1ml of this solution is

to be further diluted to a total volume of 10ml using distilled water. Formulated solutions are tested at specific wavelengths using UV visible spectroscopy [38].

Gel strength-

The measurement of gel strength can be conducted utilising a Rheometer. A precise volume of gel is prepared in a beaker. A probe is inserted into the gel. The variations in the load on the probe can be assessed based on the depth of immersion of the probe beneath the gel surface [39].

Sol-gel transition temperature and gelling time-

For in situ gel forming systems, it is necessary to measure the temperature and pH of the sol-gel process. The time required to detect in situ gelling is known as gelling time. The thermosensitive in situ gel must be evaluated for in situ gelling at body temperature [40].

Drug polymer interaction study and thermal analysis-

Interaction study can be determined through the use of Fourier Transform Infrared (FTIR) Spectroscopy. The nature of the interacting forces can be measured through the use of the KBr particle method. The percentage of water in hydrogel can be determined using the Thermo Gravimetric Analysis (TGA) for in situ formation. The Differential Scanning Calorimeter (DSC) is employed to identify a thermal difference between the pure active constituents used for gelation and the thermogram [41].

Gelling capacity-

Mix in situ gel with synthetic tear fluid in a 25:7 ratio (i.e., 25 µL of application volume and 7 µL of tear fluid in the eye) to determine the gelling capacity of ophthalmic products. The gelation can be evaluated visually by observing the time required for the gel to form and the time required for its dissolution [42].

Sterility testing-

The sterility testing is conducted in accordance with the IP 1996. In this experiment, the formulation will be incubated in the fluid thioglycollate medium at 30 to 35 ºC for a period of 14 days to determine the growth of bacteria, and in the soybean casein digest medium at 200 to 25 ºC to determine the growth of fungi in the formulation [43].

Accelerated stability studies-

I namber colored vials and sealed with aluminum fail the formulation is replaced for the short term. As per ICH stateguidelinestheacceleratedstabilitydoneat 40±20°Cand 75±5%RH **[44].**

***In vitro* drug release study-**

The plastic dialysis cell is employed to conduct drug release experiments on in situ preparations administered via the nasal and ocular routes. The cell is composed of two half cells, each of which contains a donor compartment and a receptor compartment. Cellulose membranes are employed to isolate these **[45]**. The donor container is filled with the preparation sol form. The assembled cell is subsequently agitated horizontally in an incubator. The fresh media can be used to replace the total volume of the receiver solution at regular intervals **[46]**. The analytical receptor media are employed to examine this receptor solution, which is then deposited in a shaker water bath at the appropriate temperature and oscillation rate. Samples are consistently extracted and examined **[47].**

Table no 03- Marketed products of Nasal *in situ* gels.

Drug substances	Indication	Dosage form	Manufacturer
Fluconazole [48]	Used to prevent the Antifungal infections	Solution (Spray)	Pfizer Limited, India
Zinc gluconate [49], Zinc acetate [50]	Used to prevent cold and the relief of cold symptoms such as sore throat, runny nose, cough and congestion	Solution (Spray)	Matrixx Initiatives, Inc

CONCLUSION

The primary focus of the present article is the examination of all variables and components of the in-situ gelling system. The in-situ gel dosage forms possess properties that contribute to patient compliance, including protracted and sustained drug release, high stability, and biocompatibility. The oral route offers the advantages of noninvasiveness and rapid action, while reliable in-situ gel offers certain advantages over injectable treatment. Bioresorbable and liquid are employed. A soluble, thermosensitive, and pH-sensitive polymer is used in nasal methods for in situ gelling systems, resulting in a more palatable drug delivery mechanism. The nasal residence period was extended by the mucoadhesive intensity and viscosity of the nasal topical gel. In order to optimise formulation research on permeability, it is possible to optimise mucoadhesive strength, pH, gelation duration, gelation temperature, rheological characteristics, and in vitro release.

Declaration by Authors

Ethical Approval: Not Applicable

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