Review Article

In Situ Gelling Nasal Drug Delivery System

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ABSTRACT:

In the nasal cavity, nasal mucosa had a high blood perfusion rate, due to this the absorption of the drug is high as compared to other routes, as well as has increased good bioavailability of drugs at the systemic circulation. To improve the nasal retention time of in-situ gel with nasal mucosa we have to use bio-compatible mucoadhesive polymer. In-situ gel nasal drug transfermethod is the type of mucoadhesive drug delivery system. When the drug is administered through nasal route then the first-pass metabolism gets reduced, had less enzymatic reaction occurrence, and prevents gastrointestinal tract ulceration. Drug release kinetic can be controlled by gelation strength of the formulation and viscosity of the *in-situ* gel formulation, so *in-situ* gel nasal drug delivery is also called a controlled and sustained drug delivery system. In-situ gels are prepared by various types of phenomenon and techniques that depend upon a different type of polymers and excipients used in the formulation.

Keywords: -Gel, *in-situ*, nasal drug delivery system.

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INTRODUCTION

Therapy through intra-nasal administration has been arecognized form of treatment in the Ayurvedic system of Indian Medicine. In modern years many drugs have been shown toachieveimproved systemic bioavailability through nasal route than by oral administration or anyother route of administration. Nasal mucosa has been considered as a potentialadministration route to achieve a quicker and higher level of drug absorption because it ispermeable to more compounds than the gastrointestinal tract because of lack of pancreatic andgastric enzymatic action, neutral pH of the nasal mucosa. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oraladministration. The greater permeability of nasal mucosa with a huge surface area affords arapid onset of therapeutic effect. The low metabolic surroundings of the nose have the potential toovercome the limitation of the oral route and matching the benefit of intravenous administration. (1)

In addition to that, nasal administration diminishes the lag time related with oral drugdelivery and offers non-invasiveness, patient comfort, self-administration, and patientcompliance, which are the barrier in intravenous drug therapy. The appealing advantage ofnasal drug delivery is the possibility of targeting the central nervous system (CNS) by by passing the blood-brain barrier (BBB). (2) The drugs absorbed nasally via olfactory epithelium arereported to enter in olfactory neurons and supporting cells and subsequently into the brain,which reduced not only the systemic toxicity of centrally acting drugs but also enhancedtherapeutic efficacy. The nasal route has received great attention as a route for vaccination. Nasal delivery of suitable antigen along with appropriate adjuvant to the nasalassociated lymphoid tissue (NALT) has the likely to induce humoral and cell mediated immunity. The nasal route is the route of choice for rapid mass immunization in developing countries. (3)

Intranasal immunization may lead to the development of local, as well assystemic immunity. Despite having a large number of advantages, the bioavailability of nasaldosage form is hindered by various physicochemical, physiological, and formulationfactors.

ANATOMY AND PHYSIOLOGY OF NOSE

The nasal cavity is distributed into two halves by the nasal septum and ranges posterior tothenasopharynx, while the utmost anterior part of the nasal cavity, the nasal vestibule, opens tothe face through the nostril Breathing and olfaction are the major function of the human nose.But it also operated as filtration and humidifiesinhaled air before reaching in lowest airway.Nasal cavity has a mucus layer and hairs, those supportive in filtrations of particles stuckininhaled air. Additionally breakdown of endogenous substances, mucociliary clearance also afunction of the nose. The human nasal cavity has a total volume of about 16 to 19 ml, and atotal

surface area of about 180 cm^2, and Thevolume of each cavity is approximately 7.5 ml, having a surface area around 75 cm^2each. (4)

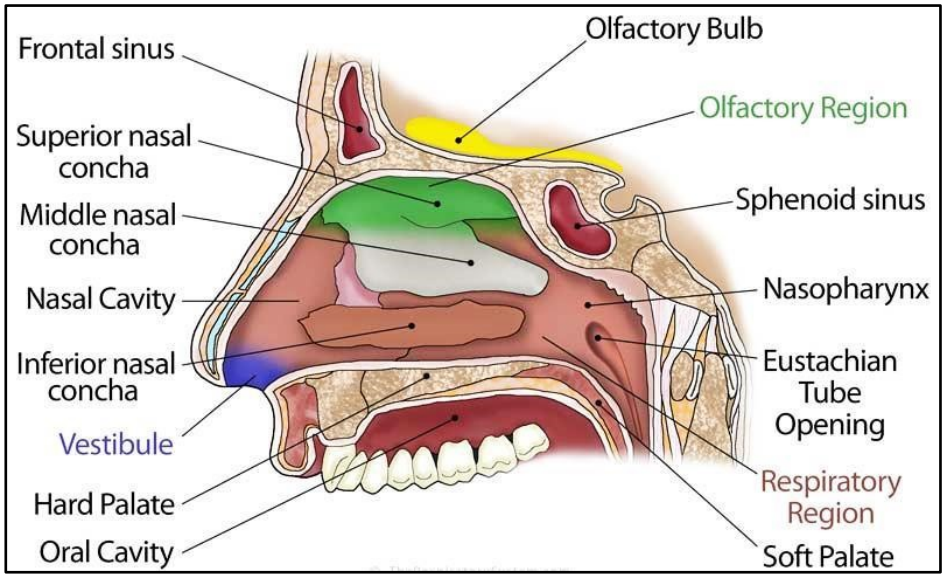
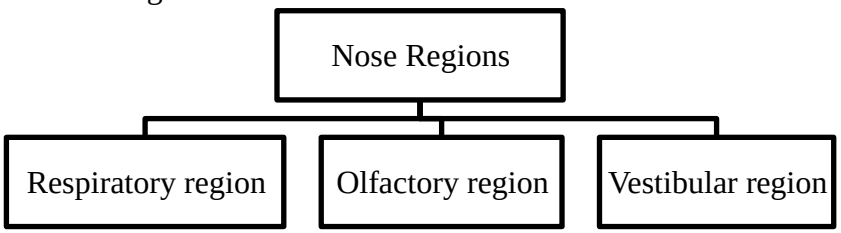


Figure 01: Internal Anatomy of Nose

Three regions can be distinguished



1. **The Respiratory region**-The respiratory region is the largest having the maximum degree ofvascularity and is chiefly responsible for systemic drug absorption. The respiratoryepithelium is composed of four types of cells, explicitly, non-ciliated and ciliated columnarcells, basal cells, and goblet cells. These cells facilitate active transport methods such as theexchange of water and ions between cells and motility of cilia (where applicable). They mayalso serve to prevent drying of the mucosa by trapping moisture. (1)
2. **Olfactory region**-It is of about 10 cm^2 in surface area and it acting as a vital role inthe transportation of drugs to the brain and the CSF. The olfactory region is situated on the roof ofthe nasal cavities, just below the cribriform plate of the ethmoid bone, which partsthenasal cavities from the cranial Cavity. The olfactory tissue is often yellow in color, in contrastto the adjacent pink tissue. Humans have quite simple noses, since the primarypurpose is breathing, while other mammals have more complex noses improved adapted for the function of olfaction. The olfactory epithelial layer predominantly encloses three cell types:the olfactory neural cells, the sustentacular (also known as supporting) cells, and the basalcells. (4)

3. The Vestibular region- It is the anterior part of the nasal cavity. Surface area is 0.6 cm 2.nasalportion is enclosed by a stratified squamous keratinized epithelial with a sebaceous gland. It isplaced at the opening of nasal passages and is answerable for filtering out the airborne particles. Drugabsorption is very tough in this region but it afforded high resistance against a toxic environment. It is deliberated to be the least important of the three regions with regard to drug absorption. (4)

Advantages of Nasal Route

Systemic nasal absorption of the drug is a new attractive alternative to parenteral drug delivery system, as it offers the following advantages. (5)

- Transnasal delivery offers direct entry of a drug into the systemic circulation, e.g., Thiomeerosal, Amastatin, Puromycin, Nifedipine, etc.
- Unlike the skin, the nasal mucosa is not fabricated from the keratinized stratum corneum. The sub-epithelial layer of the nasal mucosa with numerous microvilli is highly vascularized, with large and fenestrated capillaries facilitating rapid absorption.
- The rate and extent of absorption as well as plasma concentration *vs* time profiles are equivalent with I.V. administration.
- Avoidance of first-pass elimination, gut wall metabolism, and destruction in the gastrointestinal tract.
- Various nasal drug delivery systems are offered for user-friendly noninvasive painless application.

Limitation of Nasal Drug Delivery System

There is a risk of local side effects and irreparable damage of the cilia on the nasal mucosa, both from the drug and from the ingredients added to the dosage forms. (2)

- Certain compounds when used as absorption enhancers may disrupt and even dissolve the nasal membrane in high concentration.
- Nasal atrophic rhinitis and severe vasomotor rhinitis can decrease the capacity of nasal absorption, for example, Caerulein.
- There could be mechanical loss of the dosage form into the other parts of the respiratory tract like lungs.
- Problematic immunogenic effects might arise with the route.

Low bioavailability results from enzymatic degradation and metabolism at the mucosal site and low residence time.

Factors that affect the rate and extent of absorption of drugs via the nasal route are as follows: 1)The rate of nasal secretion.

2)Ciliary movement.

3)Vascularity of the nose.

4)Metabolism of drugs in the nasal cavity.

5)Volume that can be delivered into the nasal cavity is limited to 25 to 200 µl.

6)Diseases affecting nasal mucous membranes.

Various Dosage Forms given by Nasal Route

1. Solution and sprays

The drug solutions are administered nasally as nasal drops, sprays, and as a meter dose nebulizer. The dose of active ingredient depends on the volume of drug and the concentration of drug in the formulation. 2. Suspension

Suspensions for nasal administration are prepared by suspending the micronized drug in a micronized drug in a carrier appropriate for application to the nasal mucosa.

3. Powder

Powder dosage form of drug for nasal administration offers several advantages over liquidformulation. The chemical stability of the drug is amplified, a preservative in the formulation is not required and it is possible to administer large doses of the drug.

4. Nasal particulate drug delivery system.

New drug carrier systems are one can name soluble polymers, microparticles made of insoluble (or) biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles.

GEL

A gel is a state which exists among solid and liquid phase. The solid component comprises a threedimensional network of inter-linked molecules which immobilizes the liquid phase.

***In Situ* Gel Delivery System**

In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. *In situ* gel phenomenon is based upon liquid solution of drug formulation and converted into the semi-solid mucoadhesive key depot. It permits the drug must be delivered in a liquid form or solution form. This canbe achieved by using different polymers such as Chitosan, PVA, Poloxamer 407, Xanthangum, Gellan gum, HPMC with a different grade, Carbopol. The formation of gels depends onfactors like pH change, temperature modulation, ultraviolet irradiation, and the presence of ions,from which the drug gets released in a sustained and controlled manner. In-situ forming drugdelivery system possesses some advantages like ease of administration, simple manufacturingprocess, and improved bioavailability. Therefore, this system combines the advantages of bothsolution and gel such as ease of administration and prolonged residence time so that itdelivers improved patient compliance, dosing frequency reduces, and bioavailability. As thereare various polymers used for the preparation of such a system they needtopossessidealcharacteristics(6).

GEL PREPARATION

Drug delivery to the nasal mucosa faces several difficulties. One of these is from the effectiveclearance mechanisms present in the nose. Polymer with suitable rheological properties

canfacilitate the absorption of poorly absorbed drugs by increasing the mucoadhesivepropertiesofthe gel. Low permeability through the nasal membrane, various pathological conditionslike cold and allergic reaction which may alter the absorption. To overcome this limitation component which is used in the formulation should be minimum toxic to the nasal mucosa.Additionally, there should be the use of permeability enhancers to enhance the permeability of the macromolecule through the nasal mucosa. And also provide the maximum bioadhesive/mucoadhesive strength to minimize the clearance effect. To achieve all this novel approachof in-situ gel system were found to be effective and advantageous. (2)

Advantages

1) Drugs that are orally not absorbed can be delivered to the systemic circulation using nasal drug delivery.
2) Avoid hepatic first-pass metabolism.
3) Easy accessibility and needle-free drug application without the necessity of trained personnel facilitates self-medication, thus successful patient compliance compared to parenteral routes.
4) Drug degradation that is observed in the gastrointestinal tract is absent.
5) The bioavailability of large drug molecules can be improved using an absorption enhancer or other approaches.
6) Quick drug absorption and quick onset of action can be achieved.
7) The nasal bioavailability for minor drug molecules is good.
8) Drug possessing poor stability in GIT fluids is given by the nasal route.
9) Studies so far approved out indicate that the nasal route is an alternative to the parenteral route, especially, for protein and peptide drugs.
10) Polar compound exhibiting poor oral absorption may be particularly suited for this route of delivery.
11) Suitable for the patients, especially for those on long term therapy when associated with parenteral medication.

Disadvantages

1) Nasal cavity provides a smaller absorption surface area when compared to GIT
2) Inconvenient to a patient when compared to the oral delivery system since there is a possibility of irritation.
3) There is a risk of local side effects and irreversible impairment of the cilia on the nasal mucosa, both from the substance and from ingredients added to the dosage form.
4) There could be a mechanical injury of the dosage form into theadditional parts of the respiratory tract like lungs because of an improper technique of administration.
5) Certain surfactants used as chemical enhancers may disturb and even dissolve the membrane in high concentration.

APPROACHES FOR IN SITU GELLING POLYMERIC DRUG DELIVERY SYSTEM 1) Physiological stimuli approach

a) Temperature Induced In-Situ Gelling System: The use of biomaterial whose transitions from sol-gel is triggered by an increase in temperature is an attractive way to approach *in situ*formation. The ideal critical temperature range for such a system is ambient and physiologic temperature. In these systems, the gelling of the solution is triggered by a change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20 -25°C) and undergo gelation when in contact with body fluids (35- 37°C), due to an increase in temperature. This is probably the most normally studied class of environment-sensitive polymer systems in drug delivery research which can swell or de swell as a result of altering in the temperature of the surrounding fluid. (2) Example: chitosan, pluronic, tetronics, xyloglucans, hydroxyl propylmethyl cellulose or hypromellose (HPMC).

b) pH-induced *in situ* gel systems: All the pH-sensitive polymers contain acidic or basic groups that either accept or release protons in response to changes in environmental pH.Swelling of polymer increases as the external pH increases in the case of weakly acidic (anionic) groups also known as polyacids, but decreases if polymer contains weakly basic (cationic) groups termed as polybases. Sol to gel transition takes place when pH is raised from 4.2 to 7.4 (eye pH). At higher pH polymer forms hydrogen bonds with mucin which leads to the formulation of hydrogen network. Example: cellulose acetate phthalate (CAP) latex, carbopol, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudo latexes. (2)

2) Physical change in biomaterial approach

a) Swelling mechanism*:* *In situ* formation may also occur when a material absorbs water from the surrounding environment and expand to occur desired space. One such substance is myverol(glycerol mono-oleate), which is a polar lipid that swells in water to form lyotropic liquid crystalline phase structures.

b) Diffusion mechanism: This method involves the diffusion of solvent from polymersolution into surrounding tissue and results in precipitation or solidification of the polymer matrix. N- methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), tertahydrofuran, 2-pyrrolidone and triacetin is useful solvents for such a system.

3) Chemical reaction approach

a)Ionic cross-linking: Certain ion-sensitive polysaccharides undergo a phase transition in presence of various ions such as K+, Ca2+, Mg2+, Na+. These polysaccharides fall into the class of ionsensitive ones. A novel ophthalmic vehicle, which gels in the presence of mono- or divalent cations present in the lacrimal fluids, was used as the gelling agent. Formulation undergoes liquid-gel transition under influence of an increase in ionic strength and gel formation takes place because of complexation with polyvalent cations in a lacrimal fluid.

Example: Gelrite, gellan, hyaluronic acid, alginates.

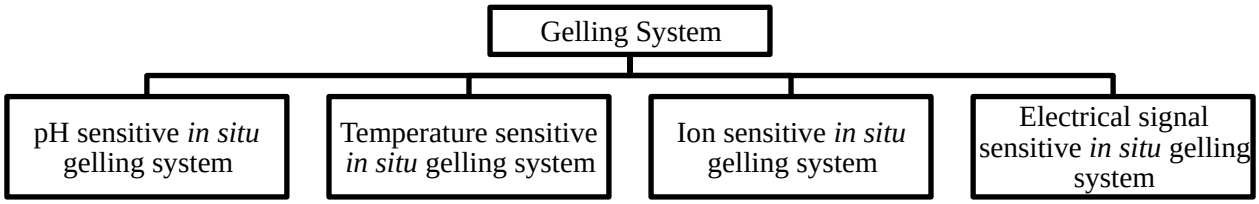
b) Photo-polymerisation: A solution of monomers or reactive macromer and initiator can be injected into a tissue site and application of electromagnetic radiation used to form a gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizablegroups on the individual monomers and macromers because they rapidly experiencephotopolymerization in the

presence of a suitable photoinitiator. Photopolymerizable systems when introduced to the desired site via injection get photocured*in situ* with the help of fiber optic cables and then release the drug for a prolonged period of time.

c) Enzymatic cross-linking: *In situ* formation catalyzed by natural enzymes has not been examined widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without the need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive

delivery systems using hydrogels that can release insulin have been investigated. (2)

CLASSIFICATION OF IN-SITU GELLING SYSTEM(7)



1. pH-sensitive *in situ* gelling system:-

In this system, there is a major role of pH in the gelling of a solution. Gelling is triggered by a change in or shifts in pH when the pH is raised from 5-7.4. At higher pH polymers forms a hydrogen bond with mucin, this leads to hydrogel formation.

Mechanism: -the entirepolymers which are pH-sensitive contain acidic or basic groups that can either accept or release proton in response to change in environmental pH. In the case of weakly basic groups swelling of a hydrogel is decreases as the external pH is increased while increases in the case of weakly acidic groups.

2. Temperature-sensitive *in situ* gelling-

This system is a liquid solution at room temperature i.e. 25-27oC and when it comes in contact with body fluid (35-37°C) undergoes gelation due to change in temperature. Temperature-sensitive gels are three types:

1. Positive temperature-sensitive gel: - It has an upper critical solution temperature such gel contracts on cooling below UCST.
2. Negative temperature-sensitive gel: - It has a lower critical solution temperature such gel contracts on heating above LCST.
3. Thermally reversible gel

Mechanism: - Upon increasing the temperature phase transitionoccurs sol to gel due to three mechanisms, increased micellar aggregation, desolvation of the polymer, and increased entanglement chain degraded. This leads to the formation of hydrogel and phase transition occurred.

3. **Ion sensitive *in situ* gelling:** The gelation is triggered by the presence i.e. Na+, Mg++,Ca++ in the fluid. This can be achieved by various polymers.

Mechanism: - The gelation is occurred by ionic interaction of polymer and divalent ions of fluid. When the anionic and cationic polymer comes in contact it converts to form a gel.

VARIOUS POLYMERS USED IN PREPARATION OF *IN SITU* GELLINGSYSTEM(6)

Polymer Mucoadhesive	Origin	Charge	Solubility	Capacity
pH-sensitive polymers				
Carbomer	Synthetic	Anionic	Insoluble	+++
Polyacrylic acid	Natural	Anionic	Insoluble	+++
Cellulose acetate pthalate	Synthetic	Nonionic	Insoluble	++
Temperature-sensitive polymer				
Poloxamer	Synthetic	Nonionic	Soluble	++
Methyl cellulose	Natural	Nonionic	Soluble	+
Chitosan	Natural	Cationic	Soluble	++
Hydroxy propyl Methyl cellulose	Natural	Nonionic	Soluble	+
Ion sensitive polymer				
Xanthan gum	Natural	Anionic	Insoluble	+
Gellan gum (Gelrite)	Natural	Anionic	Soluble	++
Sodium alginate	Natural	Cationic	Insoluble	++

Table No 01:Polymers Used in Preparation of *In Situ*GellingSystem

Ideal Characteristics of Polymers

- It should be no- toxic.
- It should be biodegradable.
- It should be biocompatible.
- It should have mucoadhesive properties.
- It should have a good tolerance

Polymers Used In pH-Sensitive *in Situ* Gelling System 1. **Carbomer Structure of Carbomer**

It is a high molecular weight, cross-linked polyacrylic acid derivative, and has a strongmucoadhesive property. Carbopol polymers are having very good water sorption properties.They swell in water up to 1000 times their original volume and 10 times their originaldiameter to form a gel when exposed to a pH environment above 4.0 to 6.0 because the pKaof these polymers is 6.0 ± 0.5. As the Carbomer concentration increased, it becomes acidic innature and may irritate. If there is an addition of cellulose then it will reduce polymerconcentration and improve a gelling property. Carbopol is manufactured by a

crosslinkingprocess. Depends on the degree of cross-linking and manufacturing conditions, variousCarbopol grades are available. Each grade is having its significance for its usefulness inpharmaceutical dosage forms which include Carbopol 934 and Carbopol 981 mostly used fora gelling purpose.

Mechanism: -The mucoadhesive property is due to electrostatic interaction or hydrophobic interaction, hydrogen bonding. It is an acidic molecule. When dispersed in water, the carboxylic group of the molecule partially dissociates and forms a coil. As it is a pH-sensitive polymer, an increase in pH of solution results in swelling of the polymer. The gelling effect is activated in two stages, neutralization of solution by addition of, sodium hydroxide or potassium hydroxide, triethanolamine.

2. **Polycarbophil**

It is lightly cross-linked polyacrylic acid having excellent mucoadhesive property. The gelling of the polymer also depends on the pH of the solution.

Mechanism: - It is insoluble in water but its swelling capacity in a neutral medium permits the entanglement of a polymer chain with a mucus layer. The carboxylic acid group of polycarbophilbinds to mucin by hydrogen bonds. Cellulose acetate latex (CAP latex) another pHsensitive polymers these are flowing liquid at pH 4.8 and gel at pH 7.4.

Polymers Used In Temperature Sensitive Gelling System:

1. Cellulose Derivative Structure of HPMC

Properties: Cellulose is composed of repeating β-(1, 4)-D-glucopyranose units in the glucan chain. Natural polymers like HPMC, MC, HPC, and EC exhibit temperature-sensitive sol-gel phase transition. When the temperature decreases cellulose materials will increase its viscosity while its derivatives like HPMC, MC will increase its viscosity when the temperature is increased. MC is composed of native cellulose with an alternate methyl substitution group on its chain. At low temperature (30ºC) solution is in liquid form and when the temperature is increased (40-50ºC) gelation occurred.

Mechanism: - Cellulose solution is converted into gelation by hydrophobic interaction between molecules containing methoxy substitution. At high temperature, polymers lose their water of hydration whereas at low temperatures, molecules are hydrated and little polymer-polymer interaction occurs.

2. Poloxamer Structure of Poloxamer

Poloxamer is a water-soluble tri-block copolymer consisting of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration.

Properties: Poloxamer commercially also known as Pluronic® and has good thermal setting property and increased drug residence time. It is used as a gelling agent, and solubilizing agent.

Poloxamer gives colorless, transparent gel. Depending upon the ratio and distribution of hydrophilic and hydrophobic chain several molecular weights available, having different gelling properties.

PoloxamergradesWeight	Poloxamer Molecular
124	2200

188	8400
237	7959
338	14600
407	12600

Mechanism: It consists of central Polypropylene oxide (Hydrophobic part) surrounded by Polyethylene oxide (Hydrophilic part). At room temperature (25ºC), it behaves as a viscous liquid and is transformed into a transparent gel when temperature increases (37ºC). At low temperature, it forms a small micellar subunit in solution, and increases in temperature results increase in viscosity leads to swelling to form a large micellar cross linked network.

3. Xyloglucan

Structure of Xyloglucan

Xyloglucan is composed of (1,4)-β-D- glucan backbone chain(GLC) with (1,6)-α-D- xylose branches (XYL), partially substituted by (1-2)-β-D- galactoxylose (GAL). It is water-soluble hemicelluloses obtained from vascular plants and it exhibit thermally responsive behavior when more than 35% galactose residues are removed.

Properties: Xyloglucan is consists of three different oligomers like hepatasaccharide, octasaccharide, nonasaccharide, which differ in the number of the galactose side chain. It is nontoxicity, biodegradable and biocompatible property. Like poloxamer, it exhibits gelation on heating refrigerator temperature or cooling from a higher temperature. But the difference is xyloglucan forms gel at lower concentration (1-2% wt).

Mechanism of gelling action: The native form of xyloglucan does not show gelation, its dilute solutions form sol-gel transition on heating due to partial degradation of β- galactosidase. The transition temperature is inversely related to galactose removal ratio and polymer concentration.

4. Chitosan Structure of Chitosan

Chitosan is a natural polymer obtained by deacetylation of chitin, it is a cationic polysaccharide consisting of copolymers of glucosamine and N-acetyl glucosamine. Chitosan has mucoadhesive property due to electrostatic interactions between positively charged amino groups and negatively charged mucin. It is non-toxic, biocompatible, biodegradable polysaccharide, and having bioadhesive.

Mechanism: Chitosan has mucoadhesive property is due to the formation of ionic interaction between the positively charged amino groups of chitosan and negatively charged sialic acid residues of mucins, depends on environmental pH because of its bioadhesive, hydrophilic, good spreading properties.

Polymers used for ion-sensitive *in situ* gelling system:

1. Deacetylatedgellan gum (Gelrite)

Gellan gum is an anionic heteropolysaccharide, secreted by microbe Sphingomonaselodea.It consists of glucose, rhamnose, glucuronic acid, and are linked together to give atetrasaccharide unit. **Properties:** Gelrite is Deacetylatedgellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Upon installation, gelrite forms gel due to the

presence of calcium ions. The gelation involves the formation of double-helical junction zones followed by aggregation of the double-helical segment to form three dimensional networks bycomplexation with cations and hydrogen bonding with water. Because of its thixotropy, thermoplasticity, pseudoplasticity are widely used in the food industry.

Mechanism: Gellan gum produce a cation induced *in situ* gelation (Ca2+, Mg2+, K, Na+) due to the cross-linking between negatively charged helices and mono or divalent cations (Na+, Ca+, Mg+). Divalent ions are superior to promoting gelation as compared to monovalent cations. Gelation prolongs the residence time of the drug at the absorption site and bioavailability of the drug is increased.

2. Sodium Alginate

Properties: Sodium alginate is a salt of alginic acid and removed from brown algae. It is alinear block polysaccharide containing of two type monomers β-D-Mannuronic acid and α-L-glucuronic acid residues joined by 1, 4 glycosidic linkages. It is biodegradable and non-toxicand exhibits good mucoadhesive property due to its carboxylic group.

Mechanism: The monomers of alginate (β-D-mannuronic acid (M) and α-L-glucuronic acid (G) areorganized as M-M block or G-G block with alternating sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties resulting in the creation of a homogenous gel. Mechanical strength and porosity of hydrogel depend on G: M ratio, type of crosslinker used, and concentration of alginate solution.

Advantages

- Avoids degradation of a drug resulting after hepatic first-pass metabolism
- Avoids degradation of the drug in the gastrointestinal tract resulting from acidic or enzymatic degradation, results in speedy absorption and onset of action and this result in greater bioavailability thus uses lower doses of a drug.
- Easily accessible, non-invasive route.
- Self-medication is possible through this route.
- Direct transport into systemic circulation and CNS is promising.
- Offers a lower risk of overdose.
- Does not have any complex formulation requirement.

Limitations

- A volume that can be delivered into the nasal cavity is restricted to 25 –200 µl only.
- High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa).
- Adversely exaggerated by pathological conditions.
- Large interspecies variability is observed in this route.
- Normal defense mechanisms like mucociliary clearance and ciliary beating affect the permeability of the drug.
- An enzymatic barrier to the permeability of drugs.
- Irritation of nasal mucosa by drugs.
- Limited understanding of mechanisms and less developed models at this stage.

EVALUATION OF FORMULATION(5)

1)**Clarity:** The clarity of *in situ* gel was examined visually under dark background.

2)**pH of the gel:** The normal range of nasal mucosal pH is 6.2 to 7.0 pH. The suitable pH of the nasal formulation is in the range of 5.5 to 7. For defining the pH of the formulation of nasal in-situ gel, taken 1 ml quantity of each formulation transported into a different beaker and diluted it with distilled water up to 25 ml and then pH of each formulation was determined by using pH meter.

3)**Drug content:** 1 ml of the formulation was taken in a 10 ml volumetric flask and then it was diluted with 10 ml of distilled water then volume adjusted to 10 ml, 1 ml from this solution again diluted with distilled water up to 10 ml. After this absorbance of the organized solution was measured at a certain wavelength of the drug by using U.V visible spectrophotometer.

4)**Viscosity measurement:** Viscosity of nasal *insitu* gel was measured by using (cone and plate viscometer) programmable Brookfield viscometer. The viscometer was equipped with the temperature control unit and the sample was equilibrated for 10 min before the measurement.Theviscosity of nasal *insitu* gel was recorded at various temperatures from 4°C to 40 °C respectively against increasing the shear.

5)**Measurement of gelation temperature:** Thegelation temperature was designated by the miller &Donovan technique. In this phase transitionhappened from a liquid phase to a gel phase. In this 2 ml *insitu* gel transferred to test tube andpositioned into a water bath then the temperature of the water bath increased slowly and constantly. The gelwas allowed to equilibrate for 5 minutes at each setting, and then formulation was examined forgelation. When the meniscus would no longer move upon tilting to 90°, this is known as agelation temperature.

6)**Determination of MucoadhesiveStrength:**Mucoadhesive strength is known as the force todetach the *insitu* gel formulation from nasalmucosal tissue, for determining themucoadhesive strength we use modified specialchemical balance. A small section of the nasalmucosa of a goat was cut & tied or fixed on 2 glassvial with the help of rubber band or thread andstored it at 37°c ±2°c for 10 minutes and then50mg of the gel was placed on the first vial and it placedbelow the height-adjustable balance, while onanother hand second vial was fixed in an invertedposition to the underside of the same balanceafter this height both vials were adjusted andcome in intimate contact for 5 minutes to ensurethe contact between nasal mucosal tissue and the*insitu* gel formulation. Then weight was put offon the other side of balance until vials gotdetached, it was expressed as the strength or stress indyne/cm².

A. Stress is calculated by the formula:

Detachment Stress (dyne/cm²) = M × G ÷ A

Where,

M = wt required for detachment of two vials in gm

G = acceleration due to gravity A = Area of tissue exposed.

7)***In vitro* Diffusion Study of *In situ* Gel:** Franzhaving capacity 2.4 diameters and 15 ml diffusioncell was used for in vitro diffusion study of *insitu*gel. Dialysis (.22µm pore size) or

cellophanemembrane (12000-18000 molwt) with diffusionarea .8cm² used.60 ml of phosphate buffer (6.4-6.6pH) was prepared and the membrane was soakedwith phosphate buffer (6.4- 6.6 pH), after thistemperature was maintained at 37°C±0.5°C, afterthis phosphate buffer placed into the acceptorchamber and gel containing drug equivalent to10 mg was placed in donor chamber, atpredetermined time point, 1ml sample waswithdrawn from acceptor chamber and thenreplaced the sample volume with an equal amountof phosphate buffer after each sampling process,for a period of 300 minutes, after each sampling,the samples were suitably diluted and measuredspectrophotometrically at a specific wavelength of a drug. The concentration of the drug was determinedwith the help of the previous calibration curve.

8) ***In vitro* Permeation Study of *Insitu* Gel: -** Tocheck permeation of drug and capacity of permeation enhancer which was added inthe formulation. Fresh nasal tissue section of the goat obtains from the slaughterhouse. Tissue wasinserted in the diffusion cell. A gel containing drugequivalent to 10 mg was placed in donorchamber, at a predetermined time point, 1mlsample was withdrawn from acceptor chamberand replacing the sampled volume with the sameamount of phosphate buffer, for a period of 300minutes, after each sampling, the sample was suitably diluted and measuredspectrophotometrically at a specific wavelength of a drug.

Marketed Products

Drug substance (product name)	Indication	Dosage form	Manufacturer
Salmon calcitonin(karil 200 I.E.)	Osteoporosis	Solution (spray)	Novartis pharma
Desmopressin (minirin nasen spray)	ADH	Solution (spray)	Ferringazacimitted
Buserelin (profact nasal)	Buserelin	Solution (spray)	Aventis pharma
Nafarelin (synarela)	Endometriosis	Solution (spray)	Pharmacia
Oxytocin (syntocinon)	Lactation	Solution (spray)	Novartispharma
Protirelin (antepan nasal)	Thyroiddiagnostic	Solution (spray)	Aventis pharma

Table No 02: Marked products.

APPLICATIONS

An *in situ* gel system for nasal delivery of mometasone furoate was developed & evaluated for its efficacy for the treatment of allergic rhinitis.gellan gum & Xanthium gum were used as *in situ* gel-forming polymers.animal studies were conducted using an allergic rhinitis model & the effect of *in situ* gel on antigen-induced nasal symptoms in sensitized rats was observed. *in situ* gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation Nasonex (mometasone furoate suspension 0.05 percent). Intact citiated respiratory epithelium & normal goblet cell appearance indicated from histopathology of rat nasal cavity proved thatthese formulations were safe for nasal administration.thermoreversible gel formulations of flunarizine

hydrochloride for improved drug residence time in the nasal cavity have been investigated.the formulations so prepared were in the liquid state at 4^{o}C but turned into a gel at the temperature of the nasalcavity.poloxamer 407 was used as the polymer which exhibited the phase transition behavior.inclusion complexes using B –cyclodextrin were prepared for increasing the solubility of flunarizine in nasal secretion.the prepared formulations were characterized for drug loading, content uniformity, in vitro drug diffusion, adhesion strength, gel strength, viscosity & gelation point. The formulations exhibited a drastic increase in the viscosity at the temperature of 37^{o}C indicating their possible use as *in situ* gelling release possibly due to an increase in the solubility & dissolution rate of flunarizine hydrochloride.

CONCLUSION

Nasal drug delivery is a novel platform & it is a promising alternative to the injectable route of administration. There is a possibility soon that more drugs will come into the market in the form of nasal formulation intended for systemic treatment. The development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetes, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. The bioavailability of nasal drug products is one of the major challenges in nasal product development. In contrast, a huge amount of money is investigated by pharmaceutical companies in the development of nasal products, because of the growing demand for nasal drug products in the global pharmaceutical market. So for the avoidance of side effects & improve the effectiveness of nasal products we should pay attention to basic research in nasal drug delivery.

FUTURE PROSPECTS

Nasal Drug delivery system is a novel system of delivering a drug through the nasal route, as this route has more advantages than conventional dosage form, and delivery of target-specific drug delivery is possible through nasal drug delivery system. Delivery of drugs to the brain is also possible as to target brain drug must cross different barriers and when nasal drug delivery is considered that time number of barriers are decreased as this route provide an easy route of administration of a drug to the brain.

Different category of drugs which have different phytochemical properties can be combined with polymers to form gel-based drug delivery system which helps mainly to deliver a drug at mucus surface such as a nasal cavity, where moisture plays an important role. This also helps to avoid the first-pass effect so drugs which should act immediately can be given through nasal route of administration to have immediate action, gen form of drug delivery also help for maintaining controlled and sustained drug delivery system hence prolonged delivery of drug can be possible.

Different types of vaccines such as multiple-dose vaccines and a single shot vaccine can be administered through the nasal route of drug delivery.

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