



REVIEW ON IN SITU GEL A NOVEL NASAL DRUG DELIVERY SYSTEM

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ABSTRACT

The oral route is most preferred and common technique for oral administration of drug in the body, but due to certain limitation such as absorption of drug, hepatic first-pass metabolism, drug targeting to particular organ can cause problem for administration through oral route. To overcome these types of problem as well as for improvement of drug safety and efficiency a novel approach is developed for delivery of drug i.e. In-situ Nasal Drug Delivery System. Nasal route is suitable for those drugs whose oral administration is problematic due to gastric irritation. The present review focused on anatomy of nasal system and criteria required of drug candidate to prepare a gel i.e. In-situ gel. Approaches towards various formulation of in-situ gel with respect to temperature, pH and physiochemical condition. The main role of polymers like Carbopol-934, PEG, Sodium alginate,

Poloxamer, Pectin, Cellulose etc. in body, absorption of drug by various methods. The in-situ gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. Various evaluation parameters which is consider during preparation of in-situ gel.

KEYWORDS: In-situ drug delivery, Polymers, Approaches, Formulation, Evaluation.

INTRODUCTION

Oral drug delivery is the most desirable route for the drug administration. Whenever systemic effects are indented but oral bioavailability of some compounds has promoted the search of more effective route for the systemic delivery. Transmucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal mucosa is the major

route of administration to achieve faster and higher level of drug absorption. ^[1] Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route, this is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism and readily accessibility. ^[2] Nasal mucosa as an alternate route to achieve faster and higher drug absorption. Knowledge of the nasal mucosa high permeability and use of the nasal route for drug administration can be traced to ancient times. Realization of the nasal mucosa as a therapeutically viable alternate route came in the last two decades. The nasal mucosa itself and the drug delivery systems affect drug absorption through the nasal route, is invaluable. A stable, safe and effective nasal product can be developed through appropriate and adequate preformulation studies of drug. ^[3] In the last few years, the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs, especially those which are ineffective orally and must be administered by injection.

Gel^[4]

Gel is the state which exists between solid and liquid phase. The solid component comprises a three dimensional network of inter-linked molecules which immobilizes the liquid phase.

In Situ gel^[5]

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 based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot.

Principle of Gelling^[6]

Main principle of In-situ gelling for nasal formulation is to be applied in nasal fluid. In this process after administration of drug solution is converted into gel in nasal cavity.

Nasal Drug Delivery System^[7]

Intranasal delivery is mainly offers potential an alternative viable for various drugs delivery. It is suitable for local and systemic delivery of diverse therapeutic compounds. Hence there have been many investigations involving the nasal cavity as a feasible site for the administration of much therapeutic agents. It is effective in treatment of local, systematic and CNS sites.

Local: Intranasal administration of medicines is the natural choice for the treatment of topical nasal Disorders. Among the most common examples are antihistamines and corticosteroids for rhino sinusitis, and nasal decongestants for cold symptoms. In these cases, intranasal route is the primary option for drug delivery because it allows a rapid symptom relief with less side-effect.

Systemic: The intranasal administration is an effective way to systemically delivery of drugs as an alternative to oral and intravascular routes. Consequently, the number of drugs administered as nasal formulations intended to achieve systemic effects has widely increased. Some prominent examples include analgesics [morphine], cardiovascular drugs as Propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and Ketorolac, and antiviral drugs [acyclovir].

CNS Delivery through Nasal Route: The tight junctions of the BBB surrounding the brain is one of such mechanisms, resulting in a greater transendothelial electric resistance [1500-2000 Ω .cm²] compared to that of other tissues like skin, bladder, colon, lungs [3-33 Ω .cm²]. The obstacle imposed by those brain protective mechanisms has increased the interesting developing strategies to overcome them when brain drug exposure is required. In this context over the last few years, intranasal route has emerged as a promising approach for brain delivery of drugs. The absence of gastrointestinal and hepatic pre-systemic elimination is advantage in this delivery system.

Anatomy and Physiology of Nose^[5,14]

It is essential to have a clear understanding of anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used. In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways. The human nasal cavity has a total volume of 15-20ml and a total surface area of approximately 150cm. Nose is divided into two nasal cavities via the septum. The volume of each cavity is about 7.5 ml and has a surface area around 75 cm pH of the mucosal secretions ranges from 5.0 to 6.7 in children and 5.5 to 6.5 in adults. The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. The mucus moves through nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min.

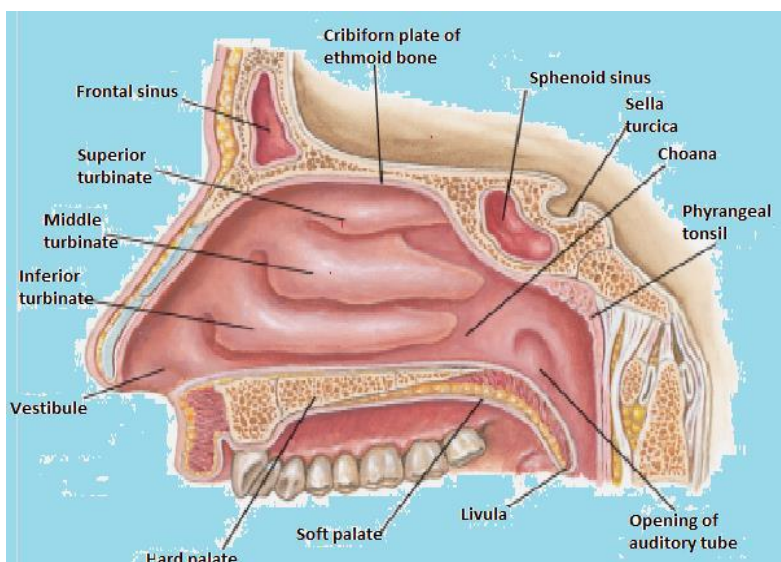


Fig. 1: Anatomy of Nasal Cavity

Three regions can be distinguished in each part

1. Respiratory region: The nasal respiratory region is the largest part of the nasal cavity, also called conchae. The respiratory region is the most important for systemic drug delivery.¹⁰⁻¹² The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells. The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each of the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically.

2. Vestibular region: Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands is responsible for filtering out the air borne particles. It is considered to be less important of the three regions with regard to drug absorption.

3. Olfactory region: The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall it is of about 10 cm² in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. When the drug is administered intranasally, it can enter into the brain via three different paths. The first one is the systemic pathway by which the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing BBB [especially lipophilic drug]. The others are the olfactory region and the trigeminal neural pathway by which drug is transported directly

from the nasal cavity to CNS [cerebrospinal fluid and brain tissue]. There are different mechanisms by which the drugs cross the olfactory membrane to reach CNS. The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism depends on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neuron.

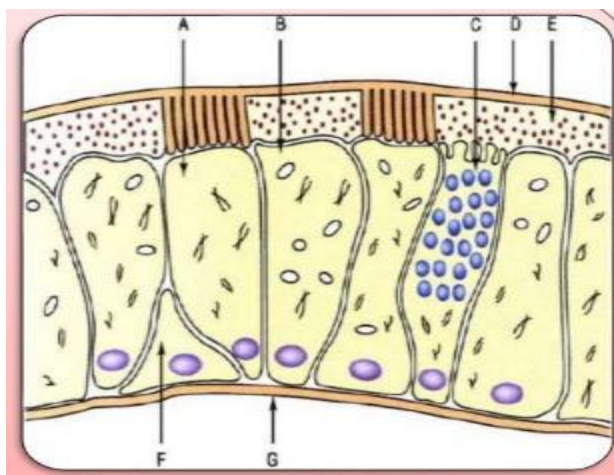


Fig. 2: Cell Type of The Nasal Epithelium Showing Ciliated Cell (A) Non Ciliated Cell (B) Goblet Cells (C) Gel Mucus Layer (D) Sol Layer (E) Basal Cell (F) Basement Membrane.

Advantages and Disadvantages of Nasal Drug Delivery System^[15,16]

Advantages

- Drug degradation is absent.
- Hepatic first – pass metabolism is absent.
- Rapid drug absorption.
- Quick onset of action.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- Better nasal bioavailability for smaller drug molecules.
- Convenient route for long term therapy.
- Minimal aftertaste
- Easy accessibility to blood capillaries.

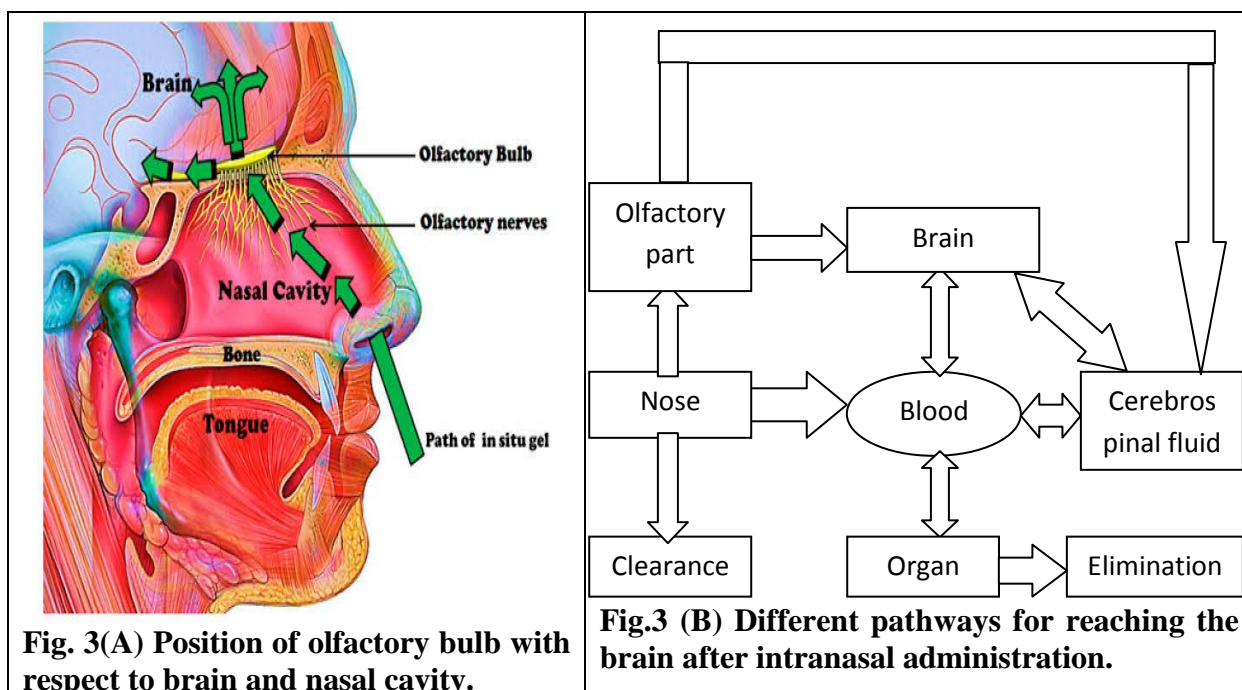
- Polar compounds particularly suited for nasal route.

Disadvantages

- High permeability of the nasal mucosa.
- Lack of adequate aqueous solubility.
- Entire dose limit volume of 25–200 ml.
- Less suitable for chronically administered drugs. For example insulin.
- Use absorption enhancers.
- Less absorption surface area is less.
- Once the drug administered cannot be removed.
- Nasal irritation.
- Delivery is expected to decrease with increasing molecular weight of drug.
- Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa.
- Nasal congestion due to cold or allergies.

Mechanism of Drug Absorption^[17]

The absorbed drugs should pass from nasal cavity to mucus layer. This is very first step of absorption. Small, uncharged drugs can easily pass through this layer but larger, charged drugs are difficult to pass/ cross it. The main principle protein of mucus is mucin which has tendency to bind to the solutes, hindering diffusion. Some additional structural changes in the mucus layer is possible as a result in environmental changes (i.e. pH, temperature).



Mainly in this process two mechanism have been predominantly used, such as

- A. First mechanism: It is also known as paracellular transport this utilizes the aqueous route of transport and but slow and passive. This route is not suitable for those drugs whose molecular weight is greater than 1000 Daltons due to its poor bioavailability.
- B. Second mechanism: It is also known also known as transcellular transport which utilizes the lipoidal route for transport of lipophilic drugs.
- C. Drugs also cross cell membranes by an active transport route which is carrier mediated or transport through the opening of tight junctions. For example Chitosan, a natural biopolymer from shell fish opening tight junctions between epithelial cells facilitate.

Factors Affecting Nasal Drug Delivery System

Factors influencing absorption are related to nasal physiology, physic chemical characteristics of drugs and formulation aspects.

1. Biological Factors

Efforts have been made to modify and explore the structural features and mechanism of nasal mucosa to increase its permeability; this is usually not available in normal physiology of nasal cavity, mainly during chronic application. These alterations could cause unintended adverse effects and result in pathological implications.

a) Structural features: Nasal epithelium mainly consists of different type cell show variety in nasal absorption and because of other factors such as presences of microvilli, cell density, surface area and number of cells. Respiratory region is most accurate and suitable for permeation of the compounds.

b) Biochemical changes: Large number of enzymes such as oxidative and conjugative enzymes, peptidases and proteases are mainly act on nasal mucus which is enzymatic barrier for delivery of drugs. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect, which hampers the absorption of drugs. Some example like the nasal P450-dependent monooxygenase system has been implicated in nasal metabolism of nasal decongestants, alcohols, nicotine and cocaine.^[18,19]

2. Physiological factors

a) Blood flow/ supply: Nasal mucosa have larger surface area and rich with blood supply which make nasal an optimum place for drug absorption. The blood flow rate influences

significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane, reaching the general circulation. Example Kao et al. stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect.^[20]

b) Nasal secretion: The mucus layer probably exists as a double layer (5 mm thick) consisting of periciliary sol phase in which the cilia beat and a superficial blanket of gel is moved forwards by the tip of the cilia. The permeability of drug through the nasal mucosa is affected by viscosity of nasal secretion. Approximately 1.5-2.1 ml of mucus is produced daily in nasal cavity. It is reported that if the sol layer of mucus is too thin, the viscous surface layer will inhibit the ciliary beating, and if the sol layer is too thick, mucociliary clearance is impaired because contact with cilia is lost. Solubility of drug in nasal secretions: a drug needs to be solubilized before it permeates. Various studies revealed that the secretion and clearance rates are reduced at night thus altering the permeation of drug. In such cases chronokinetics will dictate the pattern and rate of permeation.

c) Nasal cycle: In this process congestion and relaxation regulate the rise and fall in the amount of drug permeation process.

d) pH of nasal cavity: Nasal cavity pH in adult is 5.5-6.5 and 5.0-7.0 in infants. A greater drug permeation is usually achieved at a nasal pH that is lower than the drug's pKa because under such conditions the penetrant molecules exist as unionized form. A change in the pH of mucus can affect the ionization and thus increase or decrease the permeation of drug, depending on the nature of the drug. The ideal pH of a formulation should be within 4.5–6.5 and if possible the formulation should also have buffering capacity.^[21]

e) Mucociliary clearance and ciliary beat frequency: The main function of the mucociliary clearance system is to remove foreign substances (bacteria, allergens and so on) and particles from the nasal cavity, thus preventing them from reaching the lower airways. Normal mucociliary transit has been reported to be 12 to 15 min. Transit times of more than 30 min are considered to be abnormal, and are indicative of impaired mucociliary clearance. Reduced Mucociliary clearance (MCC) and ciliary beating (MCC) increases the time of contact between a drug and the mucus membrane and subsequently enhances drug permeation; whereas, increased MCC decreases drug permeation. Some factors affecting on MCC like drugs, hormonal changes of the body, pathological conditions, environmental conditions and formulation factors.^[21,22]

3. Pathological condition

Diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis are usually associated with mucociliary dysfunctioning, hypo or hypersecretions, and irritation of the nasal mucosa, which can influence drug permeation.

a) Environmental Condition: Temperatures in the range of 24°C cause a moderate reduction in the rate of MCC. A linear increase in ciliary beat frequency occurs with increase in temperature, which in turn influences the properties of the mucous membrane.^[21]

4. Physicochemical properties of drug

a) Molecular weight: Nasal delivery is expected to decrease with increasing molecular weight of the drug. A linear inverse correlation has been reported between the absorption of drugs and molecular weight is greater than 1000 Dalton except with the use of absorption enhancers. With the help of permeation enhancer's good bioavailability to at least 6000 Daltons can be achieved.^[23]

b) Size: Particle size and morphology are important tool for design of nasal drug delivery. Generally, particles in the 5-10 microns range should be deposited in the nostrils. Too fine particles, below five microns may be inhaled into lungs and should be avoided for nasal products while particles greater than 10µm are deposited with upper respiratory tract.^[24]

c) Solubility: It not only limits the drug absorption, it can also limit a formulator ability to formulate a product if the drug is not sufficiently soluble in the desired vehicles. From a mechanistic and thermodynamic standpoint point of view, it is important to learn about the relationship between a drug's saturation solubility and its absorption.^[3]

d) Lipophilicity: Lipophilic compounds tend to readily cross biological membranes *via* the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Some example like number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinylestradiol, have been shown to be completely or almost completely absorbed nasally in animal models. On increasing in lipophilicity, the permeation of the compound normally increases through nasal mucosa.

e) Pka and partition coefficient: According to pH partition theory, unionized species are absorbed better compared with ionized species and the same holds true in the case of nasal absorption.^[25]

5. Physicochemical properties of formulation^[26]

a) Drug concentration, dose and dose volume: Drug concentration, dose and dose volume of administration are three interrelated parameters that impact the performance of the nasal delivery system. If the drug is increasing by increasing formulation volume there may be a limit as to what extent nasal absorption will drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15ml with an upper limit of 0.20ml.

b) PH and mucosal irritancy: The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because; lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 0.1-0.2 ml/nostril.

c) Buffer capacity: Nasal formulations are generally administered in small volumes ranging from 25 to 200 μ L. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

d) Solubilisers: Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents are used such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs.

e) Preservatives: Nasal formulations usually contain preservatives to protect them from microbial contamination. Some typically used preservatives are Parabens, Benzalkonium chloride and benzoyl alcohol. Preservatives are used in small quantities and are not likely to affect drug absorption.

f) Antioxidants: Usually, antioxidants do not affect drug absorption or cause nasal irritation. Example- sodium metabisulfite, sodium bisulfate, butylated hydroxytoluene and tocopherol.

g) Humectants: Intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel based nasal products to avoid nasal irritation. Humectants avoid nasal irritation and are not likely to affect drug absorption. Examples like glycerin, sorbitol and mannitol.

h) Absorption enhancer: Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation. Once a suitable enhancer is identified, its optimal concentration should be experimentally determined. Generally, higher concentrations of enhancers are likely to result

in nasal irritation and damage to nasal mucosa. On the other hand, lower enhancer concentrations would generally provide lower or no improvement of absorption.

Properties of Nasal in- Situ Gel^[27]

It should have long residence time.

It should be low viscous.

Free flowing allow for reproducible administration to nasal cavity.

The nasal in-situ gel follows phase transition mechanism and shear forces in nasal cavity wall.

Approaches of In-Situ Gelling System^[28-31]

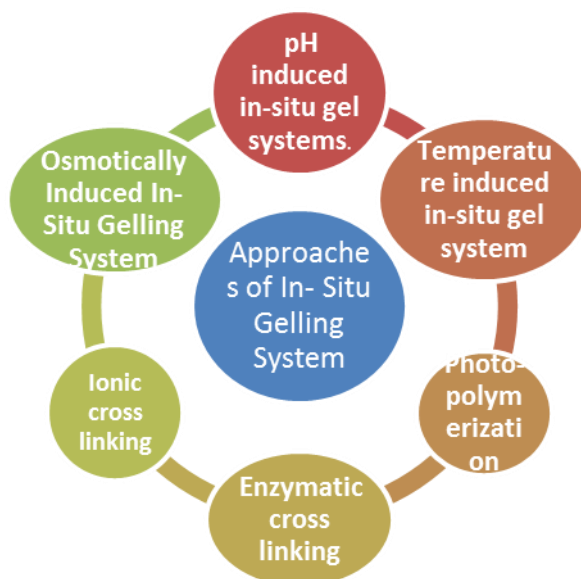


Fig. 4: Approaches of In-situ gelling system

A) Stimuli Responsive In-Situ Gelling System

Physical or chemical changes in response to small external changes in the environmental conditions.

1) Temperature induced in-situ gel system

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in-vivo and in-vitro. These hydrogels are liquid at room temperature (20°-25°C) and undergoes gelation when in contact with body fluids (35°-37°C), due to increase in temperature.

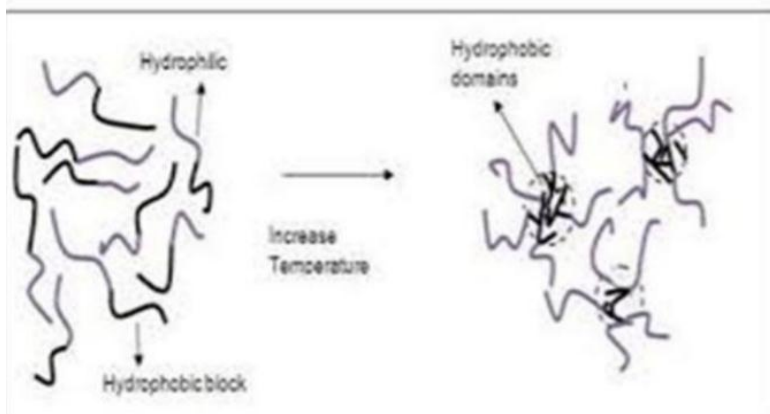


Fig. 5: Temperature induced in-situ gelling.

The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose).^[27,28]

2) pH inducing in-situ gelling system

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by change in pH. At pH 4.4 the formulation is free from is a free running solution which undergoes coagulation when the pH is raised by the body fluid to pH 7.4. The polymers which shows pH induced gelation are cellulose and its derivatives polyvinyl acetate, polyethylene glycol.^[27]

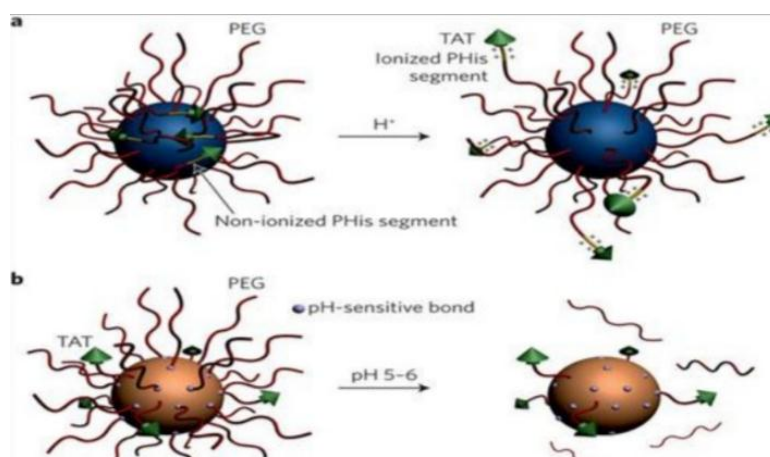


Fig. 6: pH induced In-situ gelling system.

B) Osmotically Induced In-Situ Gelling System

In this method, gelling of the solution instilled is triggered by changes in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the

gel. The aqueous polymer solution forms a clear solution forms a clear gel in the presence of the mono or divalent cations. The polymer which shows osmotically induced gelation is gellan gum, alginates.^[28]

C) Chemically Induced In-Situ Gelling System

The chemical reaction which forms in-situ gel systems are ionic crosslinking, enzymatic cross linking and photo-polymerization.^[29]

1. Ionic Cross Linking

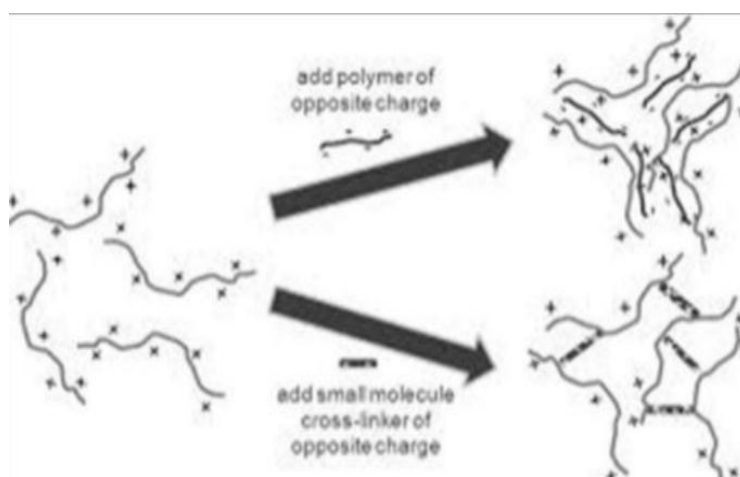


Fig. 7: Ionic Cross Linking.

Ion sensitive polysaccharides such as carragenan, gellan gum, pectin, sodium alginate undergo phase transition in presence of various ions such as K^+ , Ca^{2+} , Na^+ . These polysaccharides fall into the class of ion-sensitive ones. For example, Alginic acid undergoes gelation in presence of divalent cations example- Ca^{2+} due to the interaction with guluronic acid block in alginate chains.

2. Enzymatic cross linking

In-Situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and physicochemical approaches. For example an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

3. Photo polymerization

Photo polymerizable systems when introduced to the desired site via injection get photo cured in-situ with the help of fiber optic cables and then release the drug for prolonged period

of time. A photo polymerization, biodegradable hydro gels as a tissue contacting material and controlled release carrier. This method is utilized when gellan gum or pectin is used as a gelling polymer. At higher temperature, gellan chains dissolve in water and assume a random-coil conformation with a high segmental mobility at high temperature and remain as a solution at higher temperature. Sol—gel transition occurs on cooling gellan gum solution in the presence of ions like K^+ or Ca^{2+} . Similarly, pectin also requires higher temperature for its demethoxylation, which helps in the formation of solution or dissolving of pectin.

Methods of formulation^[32,33]

In general, two methods are used for the preparation of in site nasal gel namely.

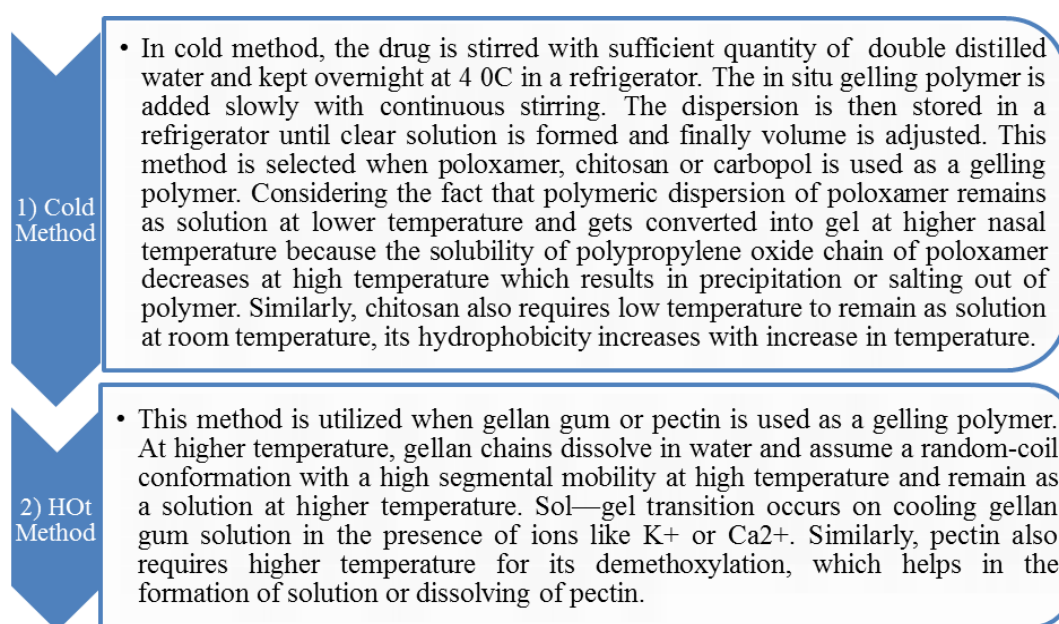


Fig. 8: Method of Formulation Nasal In-situ Gels.

Table 1: Summary of the reported studies investigated as Nasal In-situ Gel.^[34]

Polymer	Gelling agent	Drug
Poloxamer	HPMC	Diltiazem hydrochloride
Poloxamer	Carbopol 940	Carvedilol
Dillenic acid	HPMC	Felodipine
Poloxamer	Propylene glycol	Metoprolol succinate
Sodium alginate	HPMC-K4M	Metoprolol tartarate
Pluronic acid F127	Xanthium gum	Rizatriptan benzoate
Pluronic acid F127	Carbopol 934P	Sumatriptan succinate
Gellan gum	HPMC 100	Zolmitriptan
Carbopol 934	HPMC K4M	Levodopa
Poloxamer	HPMC	Ondansetron Hydrochloride
Carbopol 934	HPMC K4M	Levocetirizine
Pluronic F188	HPMC K4M	Fluoxetine HCL

Polymer used in In-Situ Gel^[35-38]

1. The polymers and its degradation products should be nontoxic and non-absorbable from the gastrointestinal tract.
2. It should adhere quickly to moist tissue and should possess some site specificity.
3. It should be a non-irritant to the mucous membranes.
4. It should possess a wide margin of safety both locally and systemically.
5. The cost of the polymer should be not too high, so that prepared dosage form remains Competitive.

Table 2: Polymers used for the preparation of In-situ Gelling System.^[38]

Polymer	Origin	Charge	Solubility	Mucoadhesive Capacity
pH Sensitive Polymers				
Carbomer	Synthetic	Anionic	Insoluble	+++
Polyacrylic acid	Natural	Anionic	Insoluble	+++
Cellulose acetate phthalate	Synthetic	Nonionic	Insoluble	++
Temperature Sensitive Polymers				
Poloxamer	Synthetic	Nonionic	Soluble	++
Methyl Cellulose	Natural	Nonionic	Soluble	+
Chitosan	Natural	Cationic	Soluble	++
Hydroxy propyl methyl cellulose	Natural	Nonionic	Soluble	+
Ion Sensitivity Polymers				
Xanthan Gum	Natural	Anionic	Insoluble	+
Gellan Gum (Gelrite)	Natural	Anionic	Soluble	++
Sodium Alginate	Natural	Cationic	Insoluble	++

Polymers used for the preparation of In-situ gelling system**A) Polymer used in pH sensitive In-situ gelling system**^[39]

a) Carbopol: Carbopol polymers are having very good water sorption property. They swell in water upto 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0-6.0 because the pKa of these polymers is 6.0 ± 0.5 . It is high molecular weight, cross linked polyacrylic acid derivative and has a strong Mucoadhesive property. If there is an addition of cellulose then it will reduce polymer concentration and improve gelling property. Carbopol 934 and Carbopol 981 are mostly used as gelling agent.

Mechanism: The Mucoadhesive property is due to electrostatic interaction or hydrophobic interaction, hydrogen bonding. It is acidic molecule. When dispersed in water, carboxylic group of the molecule partially dissociate and form a coil. As it is pH sensitive polymer, increase in pH of solution result in swelling of polymer. The gelling effect is activated in two

stages, neutralization of solution by addition of, sodium hydroxide or potassium hydroxide, triethanolamine.

B) Polymer used in temperature sensitive In-situ gelling system^[40,41]

a) **Poloxamer:** Poloxamer are water soluble tri-block copolymer consisting of two polyethylene oxide and polypropylene oxide 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 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 property.

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

C) Polymer used in ion sensitive In-situ gelling system

a) **Sodium alginate:** Sodium alginate is a salt of alginic acid extracted from brown algae. It is a linear block polysaccharide consisting 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-toxic and exhibit good Mucoadhesive property due to its carboxylic group.^[39]

Mechanism: The monomers of alginate β -D-Mannuronic acid and α -L glucuronic acid are arranged as M-M block with altering sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties resulting in the formation of homogenous gel. Mechanical strength and porosity of hydrogel depends on G: M ratio, type of cross linker used and concentration of alginate solution.

Synthetic Polymers^[42]

a) **N-isopropyl acrylamide copolymers:** Poly (N-isopropyl acrylamide) is a non-biodegradable polymer with LCST, 32°C in water and cross linked gels of this material collapse around this temperature.

b) PEG/PLGA Block copolymers: A novel concept, which combines thermo gelation, biodegradability, and no toxicity, has been proposed for an injectable gel system with better safety and longer gel duration.

Evaluation Parameters of Nasal In-Situ Gels

1) Clarity: The clarity may be determined by visual inspection under the black and white background.^[40]

2) Viscosity: The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid and may be determined with different viscometer like Brookfield viscometer, cone and plate viscometer. The viscosity of these formulations should be such that it should be patient compliance.

3) Texture analysis: The firmness, consistency and cohesiveness of formulation may be determined using texture analyzer which mainly indicates the syringe ability of sol so the formulation can easily administered in-vivo.

4) Drug content: Take 1ml of formulation and adjust to 10ml in volumetric flask and then dilute with 10ml of distilled water, 1ml from this solution again diluted with distilled water up to 10ml. after this take absorbance of prepared solution at a particular wavelength of the drug by using U.V visible spectroscopy.

5) Gel Strength: This parameter may be evaluated using a Rheometer. Depending on the mechanism of the gelling agent used a specified amount of gel is prepared in beaker, from the sol form. This gel containing beaker is raised at certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below gel surface.^[43]

6) Sol-gel transition temperature and gelling time: For In-Situ gel forming systems, the sol-gel transition temperature and pH should be determined. Gelling time is the time required for the first detection of gelation of in-situ gelling system. Thermo sensitive in-situ gel should be checked for in-situ gelling at body temperature.^[44]

7) Drug polymer interaction study and thermal analysis: Interaction study may be determined with Fourier transform infrared (FTIR) spectroscopy. During gelation process, the nature of the interacting forces can be evaluated using the technique by employing KBr pellet

method. Thermo gravimetric analysis (TGA) can be conducted for in-situ forming polymeric system to quantitate the percentage of water in hydro gel. Differential scanning calorimeter (DSC) conducted to observe if there are any changes in thermo gram as compared with pure active ingredients used for gelation. ^[45]

8) Gelling capacity: Mix in-situ gel with simulated tear fluid (in the proportion of 25:7 i.e. application volume 25 μ l and volume of tear fluid in eye is 7 μ l) to find out gelling capacity of ophthalmic product. The gelation may be assessed visually by noting the time for and time taken for dissolution of the formed gel.

9) Sterility testing: Sterility testing is carried out as per the IP 1996. Incubate the formulation for not less than 14days at 300°-350°C in the fluid thioglycolate medium to find the growth of bacteria and at 200°-250°C in soybean casein digest medium to find the growth of fungi in formulation.

10) Accelerated stability studies: Formulation is replaced in amber colored vials and sealed with aluminum foil for the short term accelerated stability at 40° \pm 20°C and 75 \pm 5% RH as per ICH state guidelines.

11) *In vitro* drug release studies: For in-situ formulations to be administered by oral, ocular, the drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed. ^[46]

CONCLUSION

In situ gels offer the primary requirement of a successful controlled release product that is increasing patient compliance. In situ gels are wonderful amalgamation of two pharmaceutical forms one solution second gel. Exploitation of polymeric in situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and

biocompatibility characteristics make the in situ gel dosage forms very reliable. Over the last decades, an impressive number of novel temperature, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use. Future use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems.

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