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# NASAL IN-SITU GEL: A NOVEL APPROACH FOR NASAL DRUG DELIVERY SYSTEM

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## ABSTRACT

Over the few decades, advances in the in-situ gel technologies have spurred development in many medical and biomedical applications including controlled drug delivery. Many Novel In-Situ gel based delivery matrices have been designed and fabricated to fulfill the ever increasing needs of the pharmaceutical and medical fields. In-Situ gel drug delivery systems are sol form before administration in the body, but once administered, undergo gelation in-situ, to form gel. The formation of gel depends on factors like temperature modulation, pH change, presence of ions from which drug get released in sustained and controlled manner. In-Situ gels exhibit the properties of linear polymer solutions outside the body (allowing easy injection) but gel In-Situ within the body, providing prolonged drug release profiles. Recently, it has been shown that many drugs have better bioavailability by nasal route than the oral route. This has been attributed to reach vasculature and highly permeable structure of nasal mucosa coupled with avoidance of Hepatic-first pass metabolism. Thus this review focuses on nasal drug delivery, various aspects of nasal anatomy and physiology, nasal absorption mechanism, and In-Situ gels evaluations.

**KEYWORDS:** Nasal In-Situ Gel, Absorption Enhancer, Nasal formulation, Mucoadhesive Drug Delivery System.

## INTRODUCTION

Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal mucosa has been considered as potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of nasal mucous.[1] Smart polymeric systems represent promising means of delivering the drugs, these polymers undergoes sol-gel transition, once administered. These systems are injectible fluids that can be introduce into body in a minimal invasive manner prior to solidifying or gelling within the desired or nasal cavity.[2] This interest has been sparkled by the advantages shown by In-Situ forming polymeric delivery systems such as ease of administration, improved patients compliance. In-Situ gel formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes, which can be convenient, which can result unacceptability, low bioavailability and passes first pass-effect.

### Nasal Drug Delivery System[1]

Intranasal delivery is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some drugs. Hence there have been many investigations involving the nasal cavity as a feasible site for the administration of much therapeutic agents.

### Anatomy And Physiology of Nose[4]

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril Breathing and olfaction are the major function of human nose. But is also functioned as filtration and humidification of inhaled air before reaching in lowest airway. Nasal cavity has mucus layer and hairs, those helpful in filtration of particles trapped in inhaled air. Additionally metabolism of endogenous substances, mucociliary clearance also functions of nose. The human nasal cavity has a total volume of about 16-19ml and total surface area of about 180cm$^2$ and is divided into two nasal cavities via septum. The volume of each cavity is approximately 7.5ml having surfaced around 75cm$^2$.[4]

**Three regions can be distinguished in each part**

**1. The Respiratory region**-The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption. The respiratory epithelium is composed of four types of cells namely non-ciliated, ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as exchange of water and ions between cells and motility of cilia. They may also serve to prevent drying of nasal mucosa.[5]

**2. Olfactory region**-It is about $10cm^2$ in surface area and it plays a vital role in transportation of drugs to the brain and CSF. The olfactory region is located on the roof of the nasal cavities, just below the cerebral form plate of the ethmoid bone, which separates the nasal cavities from the cranial cavity. The olfactory tissue is often yellow in color, in contrast to surrounding pink tissue. The olfactory epithelial layer predominantly contains three cell types: - The olfactory neural cells, the subtentacular cells and the basal cells.[5]

**3. The Vestibular region**-It is anterior part of nasal cavity. Surface area is 0.6cm.Nasal portion is covered by a stratified squamous keratinized epithelial with sebaceous gland. It is located at the opening of nasal passages and is responsible for filtering out the air borne particles. Drug absorption is very difficult in this region but is afforded high resistance against toxic environment. It is considered to be the least important of the three regions with regards to drug absorption.

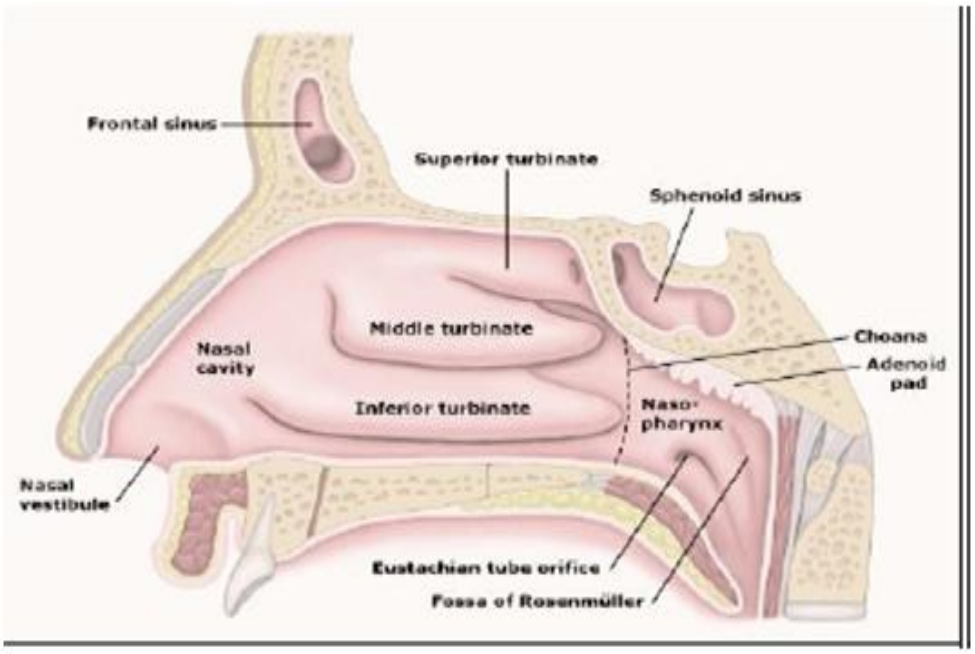


**Fig. 1 Structure of Nasal Epithelium[1]**

**Mechanism Of Drug Permeation/Absorption By Nasal Route**[6]

The absorbed drugs from the nasal cavity must pass through the mucus layer. It is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin which has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes.

**The two mechanisms are as fallows**

**First mechanism**-It involves an aqueous route of transport, which is also known as paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water soluble compounds. The molecular weight greater than 1000 Daltons show poor bioavailability.[6]

**Second mechanism**-It involves transport through a lipoidal route known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs can also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example chitosan, a natural biopolymer from shell fish opening of tight junctions between epithelial cells to facilitate drug transport.

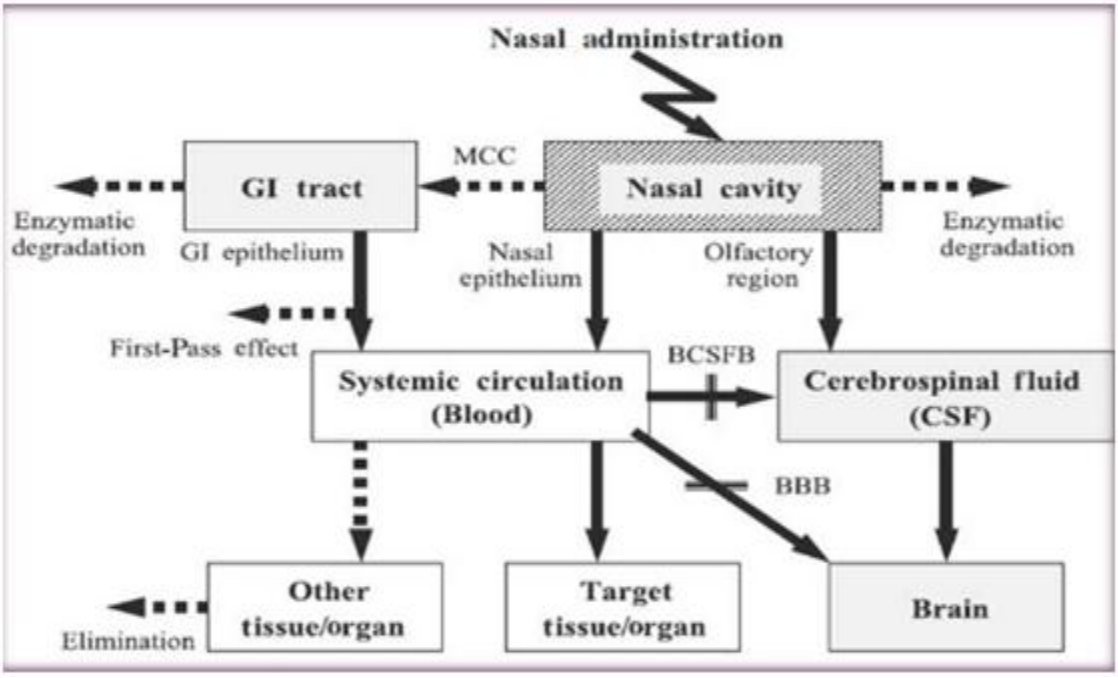


**Fig. 2 Mechanism of drug absorption by nasal route**

**Factors Affecting Nasal Drug Delivery System**[1, 4]

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

1. Biological Factors

a) Structural features.
b) Biochemical changes.
c) Physiological factors.
d) Blood flow.
e) Nasal secretions.
f) pH of the nasal cavity.
g) Mucociliary clearance and ciliary beat frequency.
h) Pathological conditions.
i) Environmental conditions.
j) Temperature.
k) Humidity.

2. Physicochemical Properties of Drugs

a) Molecular weight.
b) Size.
c) Solubility.
d) Lipophilicity.
e) Pka and partition coefficient.

3. Physicochemical Properties of Formulation

a) Dosage form.
b) Viscosity.
c) pH and mucosal irritancy.
d) Osmolarity.
e) Volume of solution applied.

4. Device Related Factors

a) Particle size of the droplet.
b) Size and pattern of disposition.

**Biological Factors**

Physiochemical factors include firstly mucociliary clearance is one of the major factor responsible for the clearance of the drugs from the nasal cavity and it involves combined action of mucus layer and cilia, tips of cilia are in contact with and transport the superficial viscoelastic mucus layer towards nasopharynx while less viscous lower layer of mucus is relatively stationary. Secondly broad ranges of metabolic enzymes are present in the nasal mucosa. This can limit bioavailability of nasally administered drugs. Moreover pathological conditions like rhinitis, common cold can also affect absorption of drugs from nasal cavity and pH of nasal cavity also affects permeation of drug. A change in the pH of mucus can affect the ionization and increase or decrease the permeation of drug depending on the nature of the drug.

**Physicochemical Properties of Drugs[1]**

Various physicochemical characteristics of drug can also affect nasal absorption of the drug.

**Molecular weight and size**

Extent of the absorption of the drug depends on molecular weight particularly for hydrophilic compounds. Nasal route is suitable for efficient delivery of the drugs up to 1000 Daltons. Absorption reduces significantly if the molecular weight is greater than 1000 Daltons except with the use of penetration enhancers. It has been reported that a good linear correlation exists between the log percentage drug absorbed nasally and the log molecular weight of water soluble compounds suggestion the participation of aqueous channels in the nasal absorption of water soluble molecules. It has been reported that particle size greater than 10µm are deposited in the nasal cavity. Particles that are 2 to 10 µm can be retained in the lungs and particles of less than 1µm are exhaled.

**Solubility and dissolution**

Drug solubility is a major factor in determining absorption of drug through biological membranes. Particles deposited in the nostrils or if they are cleared away from the nasal cavity, one may not observe the absorption of the drug.

**Chemical form**

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. For example, conversion of a drug into a salt or ester form can alter its absorption.

**Partition coefficient and pKa**

A quantitative relationship between the partition coefficient and nasal absorption is constant. As per the pH partition theory, unionized species are absorbed better compared with ionized species and same holds true in case of nasal absorption.

**Physicochemical Properties of Formulation[4]**

**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.

**Physical form of formulation**

Nasal drug absorption depends on the physical form of the formulation. The important parameter in formulation development is viscosity of the formulation. Generally a more viscous formulation will provide less efficient systemic nasal drug delivery. In nasal delivery of desmopressin, addition of the viscous agents may produce a somewhat more sustained effect. It would seem logical that more viscous formulations example- Gels should be more appropriate for locally acting drugs.

**Formulation pH**

The pH of the formulation as well as that of nasal surface can affect drugs permeation. The pH of the nasal formulation is important for following reasons,

a) To avoid irritation of the nasal mucosa.
b) To allow the drug to be available in unionized form for absorption.
c) To prevent the growth of pathogenic bacteria in the nasal passage.
d) To sustain normal physiological ciliary movement.

**Buffer capacity**

Nasal formulations are generally administered in small volumes ranging from 25 to 200µl with 100µl being the most common dose volume. 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 pH.

**Osmolarity**

Drug absorption can be affected by tonicity of the formulation. Shrinkage of the epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit ciliary activity. Low pH has similar effect as that of hypertonic solutions.

**Gelling/Viscofying agents or gel forming carriers**

Some formulations need to be gelled or made more viscous to increase nasal residence time. Increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Drug carrier such as hydroxyl propyl cellulose was effective for improving the absorption of lower molecular weight drugs but did not produce the same effect for high molecular weight peptides.

**Solubilizers[6]**

Aqueous solubility of a drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, medium chain glycerides can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers.

**Preservatives[6]**

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, benzyl alcohol are some of the commonly used preservatives in nasal formulations.

**Antioxidants**

Depending upon stability profile of a given drug in the formulation chosen, it may be necessary to use antioxidants to prevent drug degradation. Antioxidants used are sodium metabisulfite, tocopherol.

**Humectants**

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

**Absorption enhancer**[6]

When it becomes difficult for a nasal product to achieve its required absorption profile, the use of absorption enhancers is recommended. The selection of absorption enhancers is based upon their acceptability by regulatory agencies and their impact on the physiological functioning of the nose. 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.

**Table 1: Advantages of Intranasal Drug Delivery System**[6]

| Sr. No. | Advantages | Factors |
|---|---|---|
| 1 | Improving patient compliance | Needle free (painless) |
| 2 | Good penetration | In case of lipophilic and low molecular weight drugs |
| 3 | Rapid absorption and onset of action | Due to relative large surface area high vascularization |
| 4 | Avoidance of the harsh environment | Less chemical and enzymatic degradation |
| 5 | Low dose required | Free from first pass effect |
| 6 | Direct delivery of drug to central nervous system | Via olfactory region thus bypass the blood brain barrier |

**Table 2: Limitations of Nasal Drug Delivery System**[6, 7]

| Sr. No. | Limitations | Factors |
|---|---|---|
| 1 | Risk of local side effect and irreversible damage of cilia on nasal mucosa | Due to constituents added to dosage form |
| 2 | Disrupt and even dissolve the nasal membrane | Due to high concentration of absorption enhancer |
| 3 | Reduce the capacity of nasal absorption | Due to nasal atrophic rhinitis and severe vasomo rhinitis |

**Table 3: Structural features of different sections of Nasal Cavity**[3, 8]

| Region | Structural features | Permeability |
|---|---|---|
| Nasal vestibule | Nasal hairs epithelial cells are stratified squamous and keratinized sebaceous glands present | Last permeable because of the presence of keratinized cells |
| Atrium | Transepithelial region stratified squamous cells present interiorly and pseudo stratified cells with microvilli present posterior | Less permeable as it has small surface area and stratified cells are present |

| | | |
|---|---|---|
| Respiratory region | Pseudo stratified ciliated columnar cells with microvilli (300 per cell), large surface area receives maximum nasal secretion because of the presence of seromucous gland, nasolacrimal duct and goblet cells | Most permeable region because of large surface area and rich vasculature |
| Olfactory region | A specialized ciliated olfactory nerve cell for smell perception receives ophthalmic and maxillary division of trigeminal nerve direct access to cerebrospinal fluid | Direct access to cerebrospinal fluid |
| Nasopharynx | Upper part contains ciliated cells and lower part contains squamous epithelium | Receives nasal cavity drainage |

**In-Situ Gelling System**

**a) Gel-** Gel is the state which exists between solid and liquid phase. The solid component comprises a three dimensional network of interlinked molecules which immobilizes the liquid phase.[9]

**b) In-Situ 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 based upon liquid solution of drug formulation and converted into semi-solid Mucoadhesive key depot. It permits the drug must be delivered in a liquid form or solution form.[9]

In-Situ gelation is a process of gel formation at the site of application after the composition or formulation has been applied to the site. In the field of human and animal medicine, the sites, topical application sites, surgical sites and other agents are brought into contact with tissues or body fluids. As a drug delivery agent, the in-situ gel has an advantage related to the gel being formed in-situ providing sustained release of the drug. At the same time, it permits the drug to be delivered in liquid form. This new concept of production a gel in-situ was suggested first time in early 1980s. In-situ means a Latin word at the place. Both natural and synthetic polymers are used for production of in-situ gels. In-situ gel forming drug delivery systems are principle, capable of releasing drug in sustained manner maintaining relatively plasma profiles.[4]

**Principle of In-Situ Gel[10]**

Formulation of in-situ gel systems involves the use of gelling agent which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. The formulation adopted is a gellan gum or sodium alginate solution

containing calcium chloride and sodium citrate, which complexes the free calcium ions and releases them only in the acidic environment of the stomach. Gellan gum acts as gelling agent and can produce textures in the final product that vary from hard, nonelastic, brittle gels to fluid gels. The free calcium ions get entrapped in polymeric chains of gellan gum thereby causing cross linking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed by re-aggregation of double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding with water.[10]

**Importance of In-Situ Gelling System[11]**

a) The major importance is the possibilities of administering accurate and reproducible quantities compared to already formed gel.
b) In-situ forming polymeric delivery system such as ease of administration and reduced frequency of administration improved patient compliance and comfort.[4]
c) Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are installed as drops into eye and undergoes a sol-gel transition from instilled dose.
d) Liquid dosage form that can sustain drug release and remain in contact with cornea of eye for extended period of time is ideal.
e) Reduced systemic absorption of drug drained through the naso lacrimal duct may result in some undesirable side effects.[1]

**Advantages of In-Situ Gelling System[9]**

a) Increased residence time of drug in nasal cavity.
b) Decreased frequency of drug administration.
c) Results in rapid absorption and onset of action.
d) Avoid degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
e) Low dose required.
f) Minimized local and systemic circulation and CNS possible.
g) Offers lower risk of overdose of CNS acting drugs.

**Properties of Nasal In-Situ Gel[9]**

a) It should be low viscous.
b) It should be free flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as spray.
c) Nasal in-situ gel should have long residence time.
d) The nasal in-situ gel follows phase transition mechanism and to stand with shear forces in the nasal cavity wall.

**Approaches of In-Situ Gelling System[4, 12, 13, 14]**

The various approaches for in-situ gelling system,

**A) Stimuli Responsive In-Situ Gelling System[12, 13]**

1) Temperature induced in-situ gel systems.
2) pH induced in-situ gel systems.[9]

**B) Osmotically Induced In-Situ Gelling System**

**C) Chemically Induced In-Situ Gelling System**

1) Ionic cross linking.
2) Enzymatic cross linking.
3) photo-polymerization.

**A) Stimuli Responsive In-Situ Gelling System[11]**

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

**1) Temperature induced in-situ gel system[9,11]**

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. In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. 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. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose).

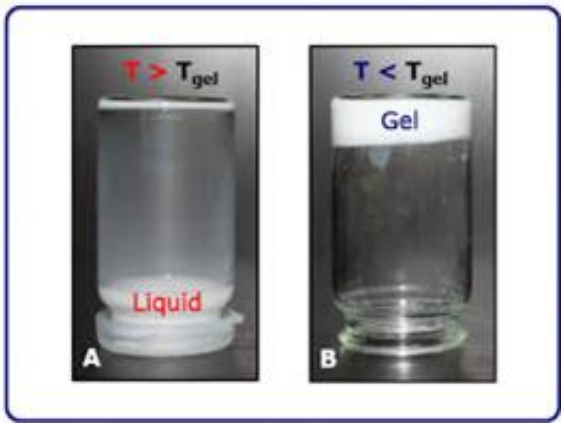


**Fig. 3 Temperature induced In-Situ gelling system.[4]**

**2) pH induced system in In-Situ gelling system[1,9]**

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.

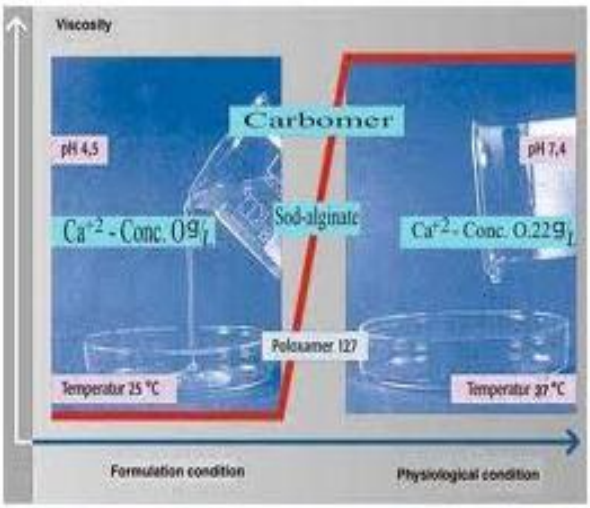


**Fig. 4 pH induced In-situ gelling system**

**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.[4]

**C) Chemically Induced In-Situ Gelling System[11]**

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

**1) Ionic cross linking**

Certain ion sensitive polysaccharides such as carragenan, gellan gum, pectin, sodium alginate undergo phase transition in presence of various ions such as k+, Ca2+, Na+. These polysaccharides fall into the class of ion-sensitive ones. For example, Alginic acid undergoes gelation in presence of divalent cations example-Ca2+ due to the interaction with guluronic acid block in alginate chains.[11]

**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.[4]

**3) Photo polymerization**

In-Situ photo polymerization has been used in biomedical applications for over more than decade. A solution of monomers can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromere because they rapidly undergo photo-polymerization in the presence of suitable photo initiator. 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.[10]

**Formulation Design[11]**

The design of in-situ formulation depends on the physiochemical properties of the drug molecules, the diseased condition for which treatment is reduced, the patient population and the marketing preference. Physiochemical factors include molecular weight, pH of tissue

fluid, mucociliary clearance. While, formulation factors include clarity, pH, gelation, spreadibility.

**Appropriate Drug Candidate Foe Nasal Delivery[14]**

1. Appropriate aqueous solubility to provide the desired dose in a 25-150 micro liter volume of formulation administered per nostril.
2. Appropriate nasal absorption properties.
3. No nasal irritation from the drug should be there.
4. A suitable clinical rational for nasal dosage forms example. Rapid onset of action.
5. Low dose generally 25mg per dose.
6. No toxic metabolites should be present and should have suitable stability characteristics.

**Table 4: Summary of the reported studies investigated as Nasal In-Situ Gel[12]**

| Polymer | Gelling agent | Drug |
|---|---|---|
| Poloxamer | HPMC | Diltiazem hydrochloride |
| Poloxamer | Carbopol 940 | Carvedilol |
| Dillinica indica | HPMC | Felodipine |
| Poloxamer | Propylene glycol | Metoprolol succinate |
| Sodium alginate | HPMC-K4M | Metoprolol tartarate |
| Plunoric acid F127 | Xanthium gum | Rizatriptan benzoate |
| Plunoric acid F127 | Carbopol 934P | Sumatriptan succinate |

**Ideal Characterstics Of Polymers Used On Nasal In-Situ Gel[1, 11]**

1. It should be non-toxic
2. It should be biodegradable and biocompatible.
3. It should have Mucoadhesive properties.
4. It should have good tolerance.

**Table 5: Polymers used for the preparation of In-Situ Gelling System[1]**

| 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 Polymer** | | | | |
| Poloxamer | Synthetic | Nonionic | Soluble | ++ |
| Methyl Cellulose | Natural | Nonionic | Soluble | + |
| Chitosan | Natural | Cationic | Soluble | ++ |
| Hydroxypropyl methyl cellulose | Natural | Nonionic | Soluble | + |
| **Ion Sensitive Polymers** | | | | |

| | | | | |
|---|---|---|---|---|
| Xanthan Gum | Natural | Anionic | Insoluble | + |
| Gellan Gum(Gelrite) | Natural | Anionic | Soluble | ++ |
| Sodium Alginate | Natural | Cationic | Insoluble | ++ |

**Various Polymers Used in Preperation of In-Situ Gelling System**

**A) Polymers used in pH sensitive In-Situ gelling system[1]**

**a) Carbomer**

It is high molecular weight, cross linked polyacrylic acid derivative and has a strong Mucoadhesive property. 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. As the carbomer concentration increased, it becomes acidic in nature and may cause irritation. 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) Temperature sensitive polymers[2,4]**

**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.[4]

**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) Polymers used of ion sensitive in-situ gelling system.**

**a) Sodium alginate[1]**

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.

**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.[1]

**Synthetic Polymers[15]**

**a) N-isopropylacrylamide copolymers[15]**

Poly (N-isopropyllacrylamide) 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 [3,15]**

A novel concept, which combines thermo gelation, biodegradability, and no toxicity, has been proposed for an injectible gel system with better safety and longer gel duration.

**Evalution Parameters of Nasal In-Situ Gels**

**Clarity[15]**

The clarity may be determined by visual inspection under the black and white background.[8]

**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.

**Texture analysis [1, 3]**

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.

**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.

**Gel strength[10]**

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.

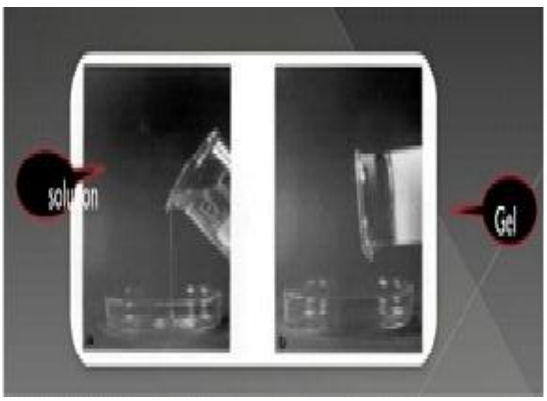


**Fig. 5 Mechanism of determination of gelling strength[23]**

**Sol-gel transition temperature and gelling time[4]**

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.

**Fig. 6 sol-gel transition temperature and gelling time[25]**

**Drug polymer interaction study and thermal analysis[5]**

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.[5]

**Gelling capacity[1]**

Mix in-situ gel with simulated tear fluid (in the proportion of 25:7 i.e. application volume 25µl and volume of tear fluid in eye is 7 µl) 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.

**Fig. 7 Measurement of gelling capacity[24]**

**Isotonicity evaluation[1, 4]**

Isotonicity is important characteristics of nasal and ophthalmic preparation. Isotonicity is maintained to prevent tissue damage or irritation of eye. All nasal preparation are subjected to isotonicity testing, science they exhibited good release characteristics and gelling capacity and the required velocity. Formulation mixed with few drops of blood and observed under microscope at 45x magnification and compared with standard marketed formulation.

**Sterility testing[1]**

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 soyabean casein digest medium to find the growth of fungi in formulation.

**Accelerated stability studies[1]**

Formulation is replaced in amber colored vials and sealed with aluminum foil for the short term accelerated stability at 40˚±20˚C and 75±5% RH as per ICH state guidelines.

**In vitro drug release studies[16]**

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.

## CONCLUSION

In situ gels offer the primary requirement of a successful controlled release product that is increasing patient compliance. 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 particular hydrogels depends on its intrinsic properties and investigated 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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