IN SITU GEL-NOVEL APPROACH FOR NASAL DELIVERY

J.U.Kute*, A. B. Darekar, R.B. Saudagar

Department of Pharmaceutics, KCT’s RGS College of Pharmacy, Anjeneri, Nasik. 422213
Maharashtra, India.

ABSTRACT
Nasal delivery is a feasible alternative to oral or parenteral administration for some Drugs because of the high permeability of the nasal epithelium, rapid drug absorption across this membrane and avoidance of hepatic first-pass metabolism. Besides this, intranasal route has also been successfully exploited for bypassing the blood brain barrier and subsequently delivering drug molecules to central nervous system. In addition it minimizes the lag time associated with oral drug delivery and offers noninvasiveness, self-medication, patient comfort and patient compliance. Prolonged drug delivery can be achieved by various new dosage forms like in situ gel. In situ forming polymeric formulations are drug delivery systems. That is in sol form before administration in the body, but once administered, undergoes gelation, in situ to form a gel. In situ gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH in situ gelforming drug delivery is a type of mucoadhesive drug delivery system. Now a day in situ gel has been used as vehicle for the drug delivery of the drug for both local treatment and systemic effect. In situ gelling system becomes very popular nowadays because of their several advantages over conventional drug delivery systems like sustained and prolonged release of drug, reduced frequency of administration, improved patient compliance and comfort.

KEYWORDS: In Situ Gel, Gelation, Mucoadhesive.
INTRODUCTION
Oral drug delivery is the most desirable route for the drug administration. Whenever systemic effects are intended 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.⁴

Majority of products available are used for treatment of allergic rhinitis, migraine, cold, pain etc. The various formulations given by nasal route includes nasal gel, spray, powders etc. Thus nasal route is the promising alternative for other drug delivery systems.⁵,⁶

ADVANTAGES OF INTRANASAL DRUG DELIVERY⁷,⁸
- Rapid drug absorption via highly vascularized mucosa
- Ease of administration, non-invasive
- Improved bioavailability
- Improved convenience and compliance
- Self-administration
- Large nasal mucosal surface area for drug absorption
- Avoidance first-pass metabolism
- Rapid onset of action
- Lower side effects
- Drugs which cannot be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system
- Convenient route when compared with parenteral route for long term therapy.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach

**DISADVANTAGES OF INTRANASAL DRUG DELIVERY**-
- Some drugs may cause irritation to the nasal mucosa
- Nasal congestion due to cold or allergies may interfere with absorption of drug
- Drug delivery is expected to decrease with increasing molecular weight
- Frequent use of this route leads to mucosal damage
- The amount of drug reaches to different regions of the brain and spinal cord varies with each agent

**ANATOMY AND PHYSIOLOGY OF NOSE**-

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 it also functioned as filtration and humidifies 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 a
function of nose. The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm$^2$, and is divided into two nasal cavities via the septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm$^2$.

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 and ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia (where applicable). They may also serve to prevent drying of the mucosa by trapping moisture.

2. **Olfactory region** - It is of about 10 cm$^2$ in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. The olfactory region is located on the roof of the nasal cavities, just below the cribriform 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 the surrounding pink tissue. Humans have relatively simple noses, since the primary function is breathing, while other mammals have more complex noses better adapted for the function of olfaction. The olfactory epithelial layer predominantly contains three cell types: the olfactory neural cells, the subtentacular (also known as supporting) cells and the basal cells.

3. **The Vestibular region** - It is anterior part of nasal cavity. Surface area is 0.6 cm$^2$. 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 it afforded high resistance against toxic environment. It is considered to be the least important of the three regions with regards to drug absorption.

**MECHANISM OF DRUG ABSORPTION BY NASAL ROUTE**

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 that include there\(^3\)

**First mechanism**-It involves an aqueous route of transport, which is also known as the 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.\(^{18,19}\)

**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 opens tight junctions between epithelial cells to facilitate drug transport.\(^{20,21}\)

**IN SITU GEL**

In situ is a Latin word which means in position. In situ gel formation of drug delivery systems can be defined as a liquid formulation generating a solid or semisolid depot after administration\(^22\). In situ activated gel forming systems are those which are when exposed to physiological conditions will shift to a gel phase. This new concept of producing a gel in situ was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or non-covalent bond formation (physical cross-linking)\(^23\). The impact of external stimuli such as temperature, pH and ionic strength, on the cross-linking of polymer chains have been studied to improve the gel strength or to induce in situ gelation. Both natural and synthetic polymers can be used for the production of in situ gels. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles\(^22,23,24\).

**ADVANTAGES OF IN SITU GEL\(^24\)**

- Prolong drug release
- Reduced systemic side effect
- Reduced number of application
- Ease of administration
- Reduced frequency of administration
- Better patient compliance
IMPORTANCE OF IN SITU GELLING SYSTEM
The major importance is the possibility of administering accurate and reproducible quantities compared to already formed gel. It increases the contact time of drug with the mucus at the site of absorption and has better bioavailability, enhancing patient compliance.\textsuperscript{25, 26}

PRINCIPLE OF IN SITU GELLING SYSTEM
The principle involving the in situ gelling of nasal formulations is that the nasal formulations imbibe in the nasal fluid after administration and forms gel into the nasal cavity. The formation of nasal gel avoids the foreign body sensation. Due to bioadhesive property the gel adheres the nasal mucosa. It acts as release controlling matrix and thus acts as sustained drug delivery system. In the nose, the mucus lower layer comes and goes around the cilia, forward in the propulsion phase, backward in the preparatory phase. At the propulsion phase, cilia extremity scrapes the upper layer of mucus penetrating it almost 0.5 mm. ciliary activity zones then occur at various intervals. Cilia situated backwards help to remove any obstacle if there is any interference in the propulsion phase. After the formation of the gel, dissolution occurs and or the mucociliary removal towards the nasopharynx occurs. Therefore there is no need to remove the dosage form after it has been depleted of drug.\textsuperscript{27}

APPROACHES OF IN SITU GELLING SYSTEM
The various approaches for in situ gelling system
1. STIMULI RESPONSIVE IN SITU GELLING SYSTEM
   - Temperature induced in situgel systems
   - pH induced in situgel systems
2. OSMOTICALLY INDUCED IN SITU GELLING SYSTEM
3. CHEMICALLY INDUCED IN SITU GEL SYSTEM
   - Ionic cross linking
   - Enzymatic cross linking
   - Photo-polymerization

1. STIMULI RESPONSIVE IN SITU GELLING SYSTEM
Physical or chemical changes in response to small external changes in the environmental condition.

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 vitro and in vivo. 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 undergo gelation when in contact with body fluids (35–37 °C), due to an increase in temperature. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc.\textsuperscript{28, 29}

**PH induced in situ gel systems**
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 a change in pH. At pH 4.4 the formulation 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 acetate phthalate (CAP) Latex, Carbomer and its derivatives polyvinylacetyldiethyl aminoacetate (AEA), Polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudo latexes etc.\textsuperscript{30, 31}

**2. OSMOTICALLY INDUCED IN SITU GELLING SYSTEM**
In this method, gelling of the solution instilled is triggered by change 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 gel in the presence of the mono or divalent cations. The polymer which shows osmotically induced gelation are gellan gum, hyaluronic acid and alginates etc.\textsuperscript{32, 33}

**3. CHEMICALLY INDUCED IN SITU GEL SYSTEM**
The chemical reaction which forms in situ gel systems are Ionic crosslinking, enzymatic crosslinking and Photo-polymerization

**Ionic cross linking**
Certain ion sensitive polysaccharides such as carragenan, Gellan gum (Gelrite), Pectin, Sodium Alginate undergo phase transition in presence of various ions such as K+, Ca2+, Mg2+, Na+. These polysaccharides fall into the class of ion-sensitive ones. For example, Alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction
With guluronic acid block in alginate chains.\textsuperscript{34, 35}
Enzymatic cross linking
In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.\(^\text{35, 36}\)

Photo-polymerization
In situ photo-polymerization has been used in biomedical applications for over more than a decade. A solution of monomers or reactive macromere and initiator can be injected into a tissue 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. 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 prolonged period of time. A photo-polymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney et al.\(^\text{33, 36}\)

MUCAOAHESIVE POLYMER USE IN NASAL DELIVERY
1. CELLULOSE DERIVATIVE
There is many pharmaceutical grade derivatives of cellulose widely used in different administration routes. Several cellulose derivatives have proved to be effective on enhancing the intranasal absorption of drugs, including soluble cellulose derivatives such as hydroxypropyl methylcellulose, hydroxypropyl cellulose (HPC), methylcellulose (MC), and carboxymethyl cellulose (CMC), and insoluble cellulose derivatives such as ethyl cellulose and microcrystalline cellulose (MCC).\(^\text{37}\)

Cellulose derivatives can markedly prolong the residence time of drugs in the nasal cavity due to their desirable mucoadhesive property. Additionally, due to their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs. For these reasons, using celluloses as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective on increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs.\(^\text{38}\)
2. GELLAN GUM
Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylatedexocellularpolysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The sol-gel transition process is induced by the presence of monovalent or divalent ions such as Na+ and Ca2+. Such as temperature and pH responsive gels, have, on the other hand, appeared more frequently in nasal drug delivery studies and have been shown to increase the residence time and improve drug absorption. A rapid gelling can be expected upon contact with the mucosa since, even at low polymer concentrations, small quantities of ions suffice for the formation of a strong gel, gellan gum which having the properties like to up take the water and it having good swelling properties and due to this it gives good bioadhesive with the GIT.

3. PLURONIC F-127
A compound which has received considerable attention is the polyoxyethylene/polyoxypropylene/polyoxyethylene triblock copolymer pluronic F127 (polaxomer 407) the thermoreversible gelation of which was demonstrated by an author. Gels of pluronic F127 have been explored for application in nasal administration. There are, however, inherent problems associated with triblock copolymers polyoxyethylene and polyoxypropylene; commercial samples are subject to formulation to formulation variability and laboratory synthesis is complicated by the so called transfer reaction which results in the presence of di block impurities. These problems may be avoided through the use of block copolymers in which oxybutylenes is substituted for oxypropylene as the hydrophobe, which can be tailor made to have the necessary sol-gel transition between ambient and body temperatures to confer in situ gelation characteristics.

4. SODIUM ALGINATE
Alginic acid is a linear block copolymersaccharide consisting of β-D-mannuronicacid (M) and α-L-guluronic acid (G) residues joined by 1, 4-glycosidic linkage. The proportionof each block and the arrangement of blocksalong the molecule vary depending on the algalsource. Dilute aqueous solutions of alginatesform firm gels on the addition of di- and
trivalent metal ions by a co-operative process involving consecutive guluronic residues in the G blocks of the alginate chain. This property has been widely exploited for the fabrication of vehicles for the sustained delivery of bioactive molecules, usually as matrix devices. It consists chiefly of sodium salt of Alginic acid; a polyuronic acid composed of β-D-mannuronic acid carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage. An alternative strategy to achieve in situ gelation of sodium alginate solutions, which was similar to that described above for the in situ gelation of gellan, has been reported. In this method gelation of a solution of sodium alginate containing Ca2+ ions is delayed until the preparation reaches the acidic environment of the stomach through complexation of the Ca2+ ions with sodium citrate. It should be noted that although the commercial preparations cited above contain sodium alginate, they do not include a source of metal ions. It is not, of course, the intention with these commercial preparations that the alginate should form a gel matrix in the stomach as in the formulations discussed, but rather should form a raft on the surface so reducing acid regurgitation.

5. POLYACRYLATE

Polyacrylates have been investigated very frequently in many drug administration routes, like nasal drug delivery systems, due to their excellent mucoadhesive and gel-forming capability. Among the pharmaceutical polyacrylates, carbomers, and polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in nasal mucoadhesive drug delivery system. Polyacrylates, capable of attaching to mucosal surfaces, can offer the prospects of prolonging the residence time of drugs at the sites of drug absorption, and ensure intimate contact between the formulation and membrane surface. Sustained release of drugs can also be obtained by using polyacrylates in nasal formulation, which result in a more stable blood concentration-time curve. Shows the use of polyacrylates in nasal drug delivery system. Besides the mucoadhesion capability, polyacrylates may also temporarily open the tight junctions between the epithelial cells during the swelling progress in the nasal cavity and improve the paracellular absorption of drugs.

5. CHITOSAN

Chitosan [2-amino-2-deoxy-(1→4)-β-d-glucopyranan] is a linear cationic polysaccharide which is obtained by a process of deacetylation from chitin, an abundant structural polysaccharide in shells of crustacea, such as lobsters, shrimps, and crabs. Due to the NH2 groups’ resultant from the deacetylation process, chitosan is insoluble at neutral and alkaline
pH. However, it can form water-soluble salts with inorganic and organic acids including glutamic acid, hydrochloric acid, lactic acid, and acetic acid. Toxicity tests have revealed that the LD50 of chitosan in mice exceeds 16 g/kg (Paul and Garside, 2000). Because of its low cost, biodegradability, and biocompatibility, chitosan has been increasingly applied as pharmaceutical excipients in oral, ocular, nasal, implant, parenteral, and transdermal drug delivery.45

Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption due to their excellent mucoadhesive properties. It was also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces. Shows various chitosan derivatives used in nasal drug delivery system. Longer clearance half-lives compared with sodium pertechnetate solution in sheep nasal cavity, respectively. In addition, many studies have proved that chitosan and its derivatives could transiently open the tight junctions between the cells and lead to the paracellular transport of drug, and Chung et al. have observed interpenetration of thermo-sensitive gels of insulin in nasal delivery by cross linking of chitosan. The preparation shows sustained release of insulin and improved pharmacological efficiency.40 Chemical and biological properties of chitosan, such as mucoadhesion and ability in enhancing nasal absorption, are determined by the types of derivatives, degree of deacetylation, and molecular weight, because chitosan is only soluble in acidic environment in which the amino groups at the C-2 position are protonated. At neutral pH, most chitosan molecules will lose their charge and precipitate from solution.43,44

Recent studies have shown that only protonated, soluble chitosan can trigger the opening of tight junctions and thereby facilitate the paracellular transport of hydrophilic mannitol. To improve the poor water solubility of chitosan, some derivatives were synthesized, such as trimethyl chitosan.

Thanou et al. reported that the trimethyl chitosan was soluble and effective on enhancing intranasal absorption even at neutral pH. N-trimethyl chitosan hydrochlorides are more mucoadhesive than unmodified chitosans and show a higher bioavailability in vivo compared with the unmodified chitosans. Due to the positive charge of chitosan in a weak acidic environment, it can also be applied to deliver the negatively charged DNA through nasal mucosa and protect them from nuclease degradation.44, 45 Compared with viral vectors; this alternative vector markedly reduced the safety risks that meanwhile result in high
transfectability. Recently, many studies show that nasal immunization with chitosan plus inactive vaccine is a potentially effective, easily administered form of vaccination. *Bordetella pertussis* filamentous hemagglutinin and recombinant pertussis toxin have shown to induce very strong systemic and mucosal immune reactions against the antigens when intranasally administrated with chitosan.\(^{37,38}\)

Bacon *et al.* have reported that chitosan solutions are able to enhance both the mucosal and systemic immune responses against influenza virus vaccines. Only in mice which received chitosan/vaccine formulation intranasally, high IgA titers in nasal washings could be found. This was not observed in mice receiving the antigen through subcutaneous injection.\(^{46}\)

**EVALUATION OF IN SITU GEL**

**Clarity**
The clarity of formulated solutions can be determined by visual inspection under black and white background.\(^{47}\)

**Viscosity**
The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) were determined with different viscometer like Brookfield viscometer, Cone and Plate viscometer. The viscosity of these formulations should be such that it should be patient compliant.\(^{48}\)

**Texture analysis**
The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringability of sol so the formulation can be easily administered in vivo.\(^{47,48}\)

**Gel-Strength**
This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a 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 the gel surface.\(^{49}\)
**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 first detection of gelation of in situ gelling system. Thermo sensitive in situ gel should be checked for in situ gelling at body temperature.50, 51

**In vitro drug release studies**

For the in situ gel formulations to be administered by oral, ocular or rectal routes, 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 technique. For injectable in situ gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed.52, 53

**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 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.

**REFERENCE**


