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An Overview on *In-Situ* Nasal Gel for Drug Delivery

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Abstract

Oral route is considered as most convenient and preferred route of administration for the systemic action. Due to poor bioavailability and hepatic first pass metabolism of certain drug, other routes are mainly preferred over oral route, such as parenteral route, transmucosal route and transdermal route. Intranasal route considered as an attractive route due to similar concentration time profile of drug as that of the intravenous route. In-situ nasal gel where drug is administered as a low viscous solution upon contact with nasal mucosa the polymeric conformation change occur and gel formation has been occur. Various triggered polymers are used for the gel formation such as poloxamer, chitosan, carbopol.

Key Words: Intranasal, thermosensitive, pH triggered, ion activated, poloxamer

INTRODUCTION

The nasal route is an important mode of drug delivery, with a growing number of products available for administration through the route for systemic and local administration. In-situ gel is a new dosage form which has been applied in nasal drug delivery recently.

Compared with liquid nasal formulation nasal in-situ gels are instilled as low viscosity solution into the nasal cavity. Upon contact with the nasal mucosa, the polymer changes conformation producing a gel. So that it not only prolong the contact time between the drug and the absorptive site in the nasal cavity, but also release drug slowly[1].

Gel is the state between liquid and solid, which consists of physically cross-linked networks of long polymer molecules, with liquid molecules trapped within a three dimensional polymeric network swollen by a solvent. Before administration, in-situ gelling system is a liquid aqueous solution and it converts into gel at physiological condition. Prolonged and sustained release of the drug is reproducible, and in-situ gel is biocompatible, with magnificent stability and reliable quantities of medication, making it more accurate.

There are various routes for in situ gel drug delivery, for, example, oral, ocular, vaginal, rectal, intravenous, intraperitoneal, etc. Gelation happens through crosslinking of the polymer chain, which can attained through covalent bond formation (chemical crosslinking) or non-covalent bond formation (physical crosslinking). Different mechanism exist which provoke the formation of in-situ gels, such as based on physiologic stimuli (e.g. temperature modifications, pH-triggered systems), those based on physical changes in biomaterials (e.g. Solvent exchange and swelling), and those based on chemical reactions (e.g. UV radiation, ionic crosslinking and ion activated systems). In this approach, there is no need for any organic solvents, copolymerization agents, or a directly applied trigger for gelation. In-situ gel formulation is executed for targeted delivery through the vaginal and rectal routes, and the nasal mucosa, circumventing the hepatic first pass metabolism, which is basically important for the delivery of proteins and peptides that are usually administered via the intravenous route because of their susceptibility to the gastrointestinal protease[2].

ANATAMY AND PHYSIOLOGY OF NASAL CAVITY [3]

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, shown in fig.i.

The three main regions in nasal cavity are nasal vestibule, olfactory region and respiratory. The surface area in the nose can be enlarges about 150cm by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinates: the superior, median and the inferior. The main nasal airway having the narrow passages usually it has 1-3mm wide and these narrows structures helps to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two area; non olfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport.

In this way the mucus layer is propelled in a direction from the anterior to-wards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of about 95% water, 2% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozyme and lactoferrin and 1% lipids. The mucous secretion gives immune protection against inhaled bacteria and viruses. It also perform number of physiological functions,

1. It covers the mucosa, and physically and enzymatically protects it
2. The mucus has water holding capacity
3. It exhibits surface electrical activity
4. It permits efficient heat transfer
5. It acts as adhesive and transports particulate matter towards the nasopharynx

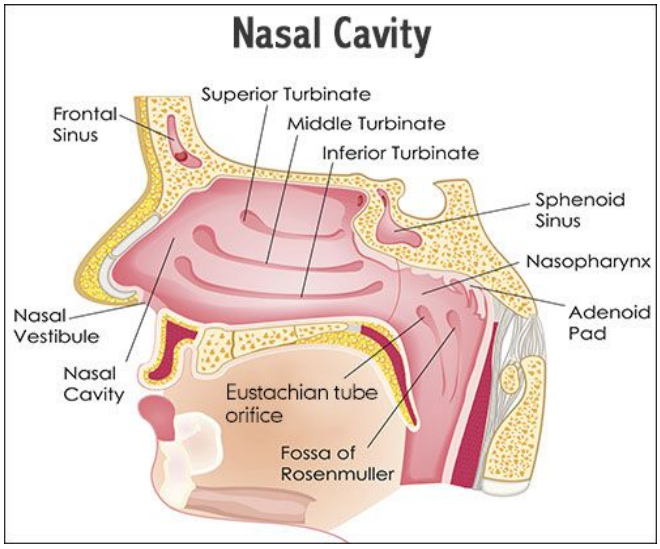

Fig. i: Anatomy of Nasal Cavity

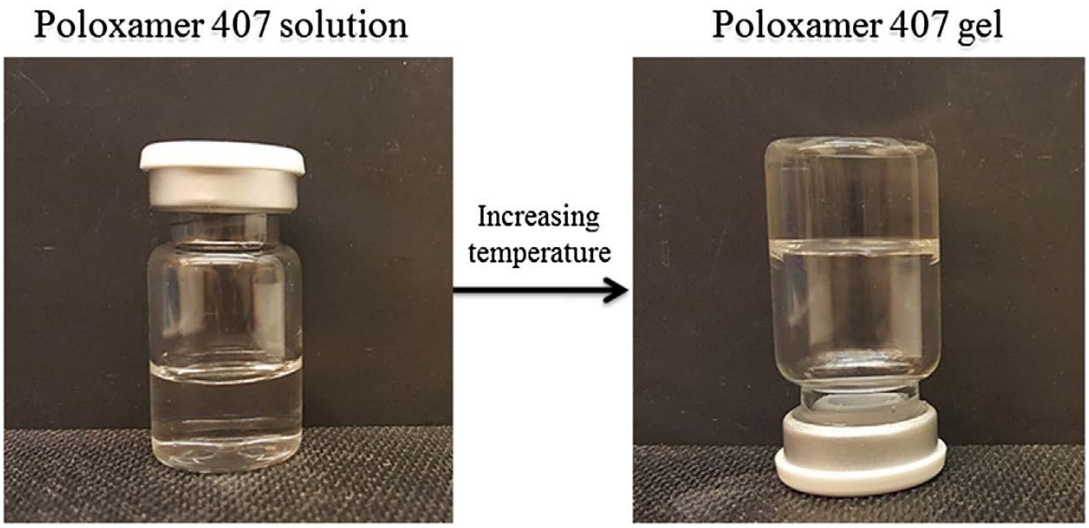

Fig.ii: Sol-Gel Transition of Poloxamer 407

MECHANISM OF NASAL ABSORPTION

1. 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 having drugs shows poor bioavailability.

2. Second mechanism:

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that shows a rate dependency on their lipophilicity. Drug also cross cell membrane by an active transport route via carrier- mediated means or transport through the opening

METHOD OF FORMULATION [4]

In generally, two methods are used for the preparation of in-situ nasal gel,

1. Cold Method
2. Hot Method

Cold Method: In this method the drug is stirred with sufficient quantity of double distilled water and kept overnight at 4 °C in a refrigerator. The in-situ gelling polymer is added slowly with continuous stirring. The dispersion is then stored in a refrigerator until clear solution is formed and finally volume is adjusted. This method is selected when poloxamer, chitosan or carbopol is used as a gelling polymer. Considering the fact that polymeric dispersion of poloxamer remains as solution at lower temperature and gets converted into gel at higher nasal temperature because the solubility of polypropylene oxide chain of poloxamer decreases at high temperature which results in precipitation or salting out of polymer. Similarly, chitosan also requires low temperature to remain as solution at room temperature, its hydrophobicity increase with increase in temperature.

Hot Method: This method is utilized when gellan gum or pectin is used as a gelling 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.

TRIGGERED IN SITU GELLING FORMATION

1. **Temperature triggered in situ gel [5,6]:**

There are some polymers which undergo large and unexpected physical and chemical changes in response to small external changes in their environmental conditions. Such polymers are called Stimuli-responsive polymers. They are also called as stimuli-sensitive, intelligent, smart or environmentally sensitive polymers. These polymers recognize a stimulus as a signal, judge the degree of the signal and then transform their chain confirmation in response.

Temperature sensitive polymers are most extensively studied class of environmentally responsive polymer systems in drug delivery. This is because temperature is relatively easy to control and also easily applicable to both in vitro and in vivo. In this system, gelling of solution is triggered by alteration in temperature, thus sustaining the drug release. These hydrogels exists in liquid form at room temperature (20-25°C) and undergo gelation when comes in contact with body fluid (35-37°C). The use biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach in situ formation. The best critical temperature range for such systems is ambient and physiologic temperature; such that clinical manipulation is facilitated and no external source of heat other than that of body is required to trigger gelation.

Temperature sensitive polymers may be,

1. Positive thermosensitive gels: This system has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling UCST.
   E.g. Polymer networks of poly (acrylic acid)
2. Negative thermosensitive gels: This system have a lower critical solution temperature (LCST) and contract upon heating above the LCST.
   E.g. poly (N-isoprophylacrylamide)
3. Thermo reversible gels
   E.g. poloxamers/pluronics, tetronics

2. **pH triggered in situ gel [7]:**

Another physiological stimulus that induces formation of in situ gel is pH. Polymers included in this class contain an acidic or a basic group that either accept or release protons when they are exposed to different environmental pH. Hence these are called pH sensitive polymers. Most of the pH sensitive polymers containing anionic group are based on PAA (Carbopol®, Carbomer) and its derivatives.

3. **Ion- activated in situ gel:**

In this type of gelation, polymer that undergoes phase transition in presence of ions. Gellan gum is an anionic polysaccharide that undergoes phase transition in the presence of monovalent and divalent cations like Ca2+, Mg2+, K+, and Na+ present in the nasal secretion.

VARIOUS POLYMERS USED IN TRIGGERED SYSTEM

- **Poloxamer [8]:**

Poloxamers are triblock copolymers with a center block of hydrophobic polypropylene oxide (PPO) flanked by two hydrophilic polyethylene oxide (PEO) blocks. Among this family of copolymers, poloxamer 407 is a non-ionic surfactant with reversible gelation properties above a particular polymer concentration and a particular temperature. The gelation phenomenon is reversible and characterized by a sol-gel transition temperature (Tsol-gel). Below Tsol-gel, poloxamer407 aqueous solutions remain fluid and the solution turns to a semi-solid material above this temperature which is shown in the fig.ii. The thermogelation is due to hydrophobic interactions between the poloxamer 407 copolymer chains. By elevating the temperature, the poloxamer 407 copolymer chains start to aggregate into a micellar structure. The formation of micelle structures is a result of the dehydration of the hydrophobic PPO repeat units and defines the initial step of gelation. Tsol-gel is concentration dependent and increases by a reduction of the poloxamer 407 concentration in aqueous solution until a lower level is reached at which point poloxamer 407 does not gel anymore.

- **Chitosan [9,10]:**

Chitosan, an amine-polysaccharide is a pH dependent, cationic polymer. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. Adding poly salts, bearing a single anionic head, like glucose phosphate salts to chitosan aqueous solution can transform the cationic polysaccharides solution into thermally sensitive pH dependent gel.

- **Carbopol:**

Carbopol is a polyacrylicacid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopol (poly acrylic acid) is a well-known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH.

- **Pectin [11]:**

Pectins are a family of polysaccharides. Low methoxypectins readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains. Although the gelation of pectin will occur in the presence of H^+ ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery.

- **Gellan gum [12]:**

Gellan gum is an anionic deacetylated, exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of 1b-l-rhamnose, 1b D-glucuronic acid and 2b D-glucose. The mechanism of gelation involves the formation of double-helical junction zones followed by aggregation of the double-

helical segments to form a 3-D network by complexation with cations and hydrogen bonding with water. Because human nasal mucosa is covered with approximately 0.1 ml mucus, which consists of sodium, potassium and calcium ions.

- **Ethyl (Hydroxyethyl) Cellulose [13]:**
  Ethyl (hydroxyethyl) cellulose (EHEC) is a non-ionic amphiphilic polymer containing ethylene oxide (EO) groups, having mixed hydrophobic (low amount) and hydrophilic structural units. EHEC shows macroscopic phase separation when the temperature is raised above the lower critical solution temperature (LCST), as the result of the intermolecular aggregation of hydrophobic domains. The presence of hydrophilic segments in more amounts in relation to hydrophobic units renders EHEC water-soluble. Semi-dilute aqueous solutions of a certain, rather hydrophobic type of the nonionic cellulose derivative EHEC have been shown to exhibit thermogelling properties in the presence of ionic surfactants.

APPLICATION OF IN-SITU POLYMERIC DRUG DELIVERY SYSTEM

Depending on the route of drug delivery in-situ drug delivery may be,

1. **Oral drug delivery system[14]:**
   Pectin, xyloglucan and gellan gum are the natural polymers used for *in situ* forming oral drug delivery systems. Although the gelation of pectin will occur in the presence of H^+ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. The potential of an orally administered *in situ* gelling pectin formulation for the sustained delivery of paracetamol has been reported.
2. **Ocular drug delivery system[15]:**
   For *in situ* gels based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, antiinflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes. So, to overcome bioavailability problems, ophthalmic *in situ* gels were developed. Aqueous solution of gellan dropped into the eye undergoes transition into the gel state due to the temperature and ionic condition (Ca^{++}) in the tear fluid. Much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug delivery. Drug release from these *in situ*gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops.
3. **Nasal drug delivery system[16]:**
   An *in situ* gel system for nasal delivery of mometasone furoate was developed and evaluated for its efficacy for the treatment of allergic rhinitis. Gellan gum and xanthan gum were used as *in situ* gel forming polymers. Animal studies were conducted using an allergic rhinitis model and the effect of *in situ* gel on antigen induced nasal symptoms in sensitized rats was observed. *In situ* gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation nasonex (mometasone furoate suspension 0.05%).
4. **Rectal drug delivery system[17]:**
   In situ gels also possess a potential application for drug delivery by rectal and vaginal route. Miyazaki *et al*. investigated the use of xyloglucan based thermoreversible gels for rectal drug delivery of indomethacin
5. **Vaginal drug delivery system[18]:**
   For a better therapeutic efficacy and patient compliance, a mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating clotrimazole-β-cyclodextrin complex was formulated for the treatment of vaginitis. Pluronic F-127 was used as an *in situ* gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxylpropylmethylcellulose to ensure long residence time at the application site.
6. **Injectable drug delivery system[19]:**
   A novel, injectable, thermosensitive *in situ* gelling hydrogel was developed for tumor treatment. This hydrogel consisted of drug loaded chitosan solution neutralized with β-glycerophosphate.

CONCLUSION

Nasal route is considered as a fast emerging route of administration for the drug which is inconvenient for oral delivery due to gastric irritation, enzymatic degradation, undergoes first pass metabolism or due to low bioavailability. So nasal route is considered as a better route of drug delivery due to the direct pass of drug into systemic circulation bypassing disadvantages of oral delivery. In-situ gelling system biodegradable, mucoadhesive polymers are used which use its physiological condition for the gelling system. Their by increase the contact time as results in the controlled delivery of the drug.

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