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Research Article

FORMULATION AND EVALUATION OF NOVEL IN SITU GEL-FORMING SYSTEMS FOR NASAL DELIVERY OF DRUG- A REVIEW

Megha Parashar[1], Dr. Ashish Jain[1] and Praveen Tahilani[2]

[1]LNCT University Bhopal
[2]Sagar Institute of research, technology &Science Pharmacy, Bhopal

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A B S T R A C T

For locally acting intranasal drugs, an extended residence time in the nasal cavity is desirable and related to a prolonged effect. A gel is a soft, solid or solid like material consisting of two or more components, one of which is a liquid, present in substantial quantity. Gels do not flow under die influence of their own weight. Reversible gels refer to those that have die capacity to make, break and modify the bonds responsible for holding the network together. Gels that do not have this capability because they are held together are termed as permanent gels. Although many gels exhibit shear-thinning behavior, they cannot be easily delivered to the nasal cavity using normal droppers and spray devices because nasal cavity is an irregularly shaped space and it has folded structure. Hiesame limitation is applicable to powdered formulations. Liquid drops given by nasal route have a low nasal residence time, which is insufficient for drug absorption and the formulation sometime gets drained in the oral cavity.

Thus it will be advantageous to use a stimulus sensitive gel system that will provide the advantages of free flowing liquid till it reaches the surface of mucous and get converted into gel form when it is in contact with mucosal surface so that it will have improved nasal residence time for effective absorption of drug. This type of system will provide the patient convenience of application of formulation. Also a sustained release formulation of this nature will reduce the frequency of drug administration and will improve patient compliance.

Poloxamer 407 (Pluronic F - 127) exhibit the phenomenon of reverse-thermal gelation, i.e., the polymer exists a mobile viscous liquid at reduced temperatures, bid forms a rigid semisolid gel network with an increase in temperature. Poloxamer is nontoxic and also it functions as surfactant and solubilizing agent. But it is reported that the rate of gelation and the temperature of the sol-to-gel transition for poloxamer 407 are concentration dependent. Thus to have a thermo reversible gel with gelation temperature in the range of 34°C - 37°C optimization is need with respect to the drug, polymer and other formulation, excipients added to it. The present project involves designing of thermo reversible gel formulations suitable for nasal administration of certain drugs.

INTRODUCTION

In the last decade *in situ* gelling systems have emerged as a novel approach in intranasal delivery of therapeutics, capturing the interest of scientific community. Considerable advances have been currently made in the development of novel formulations containing both natural and synthetic polymers. *In situ*gel drug delivery systems are in solution form before administration but once administered, undergo gelation *in situ.* 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.

Corresponding author:* **Megha Parashar
Sagar Institute of Research, Technology &Science-Pharmacy, Bhopal M.P

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*gel forming 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.

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 is 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 Delivery[7, 8]

1. Improved bioavailability.
2. This route is easy to administration & non-invasive.
3. Rapid drug absorption via highly vascularized mucosa.
4. Improved convenience and compliance.
5. Self-administration.
6. Large nasal mucosal surface area for drug absorption.
7. Avoidance first-pass metabolism.
8. Drug shows rapid onset of action.
9. Lower side effects.
10. Drugs which cannot be absorbed orally may be delivered to the Systemic.
11. Circulation through nasal drug delivery system .
12. Convenient route when compared with parenteral route for long term therapy.
13. Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

Disadvantages of Intranasal Drug Delivery

1. Some drugs may cause irritation to the nasal mucosa
2. Nasal congestion due to cold or allergies may interfere with absorption of drug
3. Drug delivery is expected to decrease with increasing molecular weight
4. Frequent use of this route leads to mucosal damage

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[9,10].The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm2, 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 cm2.

Three regions can be distinguished in each part

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[12, 13].

Olfactory region*:* 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. 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[14, 15].

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.[16, 17]

Mechanism of Drug Absorbtion 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 are

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]

Physiological factors/ barriers

Mucociliary clearance

Mucociliary clearance involves the combined actions of the mucus layer and the cilia, and is an important factor in the physiological defense of the respiratory tract against inhaled hazardous particles. The composition, function and clinical aspects of nasal mucus have been widely reviewed. It is assumed that the speed of mucociliary clearance in healthy humans is about 5 mm, although this is easily influenced by pharmaceutical excipients, airborne irritants or diseases[22, 23]. The tips of the cilia are in contact with and transport the superficial viscoelastic mucus layer towards the nasopharynx, while the less viscous lower layer of the mucus is relatively stationary. Several workers, using various in vitro or in vivo methods, have investigated ciliary beat frequency in order to evaluate the effects of drugs or formulation additives or of infections in the upper airways on the mucociliary system[24]. The cilia beat in a coordinated fashion, with a frequency of approximately 10 Hz, when measured in in-vitro studies on human nasal cilia.

Protective barriers

The first step in the absorption of drugs from the nasal cavity is passage through the mucus. Uncharged substances with small molecular weight can easily pass through this layer. However, larger or charged particles may find it more difficult to cross. Mucin, the principal protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes such as pH, temperature, etc[25]. The nasal membrane is a physical barrier and the mucociliary clearance is a temporal barrier to drug absorption across the nasal epithelium.

Enzymes

While nasal administration of drugs does avoid first pass hepatic metabolism, there is a broad range of metabolic enzymes situated in the nasal mucosa which can limit then bioavailability of some drugs, especially those containing peptides or proteins. Among the enzymes present are the oxidative phase I enzymes (e.g. cytochrome P-450 enzymes), non-oxidative enzymes, conjugative phase II enzymes and proteolytic enzymes such as endo-and exo-peptidases. The nasal enzyme population and/or activities vary extensively among different species[26]. However, the level of activity seems to be lower for nasal enzymes than for those in the gastrointestinal tract or liver, on the basis of the amount of tissue involved.

***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[27]. *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)[28].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 canbe used for the production of *in situ*gels. *In situ*gel forming drug delivery systems is principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles[29-31].

Advantages of In Situgel[31]

1. Prolong drug release
2. Reduced systemic side effect
3. Reduced number of application
4. Ease of administration
5. Reduced frequency of administration
6. 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[32].

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 bioad hesive 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[32].

Approaches of in Situ gelling System

The various approaches for *in situ* gelling system

Stimuli Responsive In Situ gelling System

- ✓ Temperature induced *in situ* gel systems
- ✓ pH induced *in situ* gel systems

Osmotically induced in situgelling system

Chemically induced in situgel system

- ✓ Ionic cross linking
- ✓ Enzymatic cross linking
- ✓ Photo-polymerization

Stimuli Responsive in Situ gelling System

Stimuli responsive *in situ* gelling system is prepared by 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 anincrease 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.[33,34]

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.[35, 36]

Osmotically Induced In Situgelling 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 showsosmotically induced gelation are gellan gum, hyaluronic acid and alginates etc.[37,38]

Chemically Induced In Situgel System

The chemical reaction which forms *in situ*gel systems are Ionic cross-linking, enzymatic cross linking 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.[39,40]

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, anenzymatic process operates efficiently under physiologic conditions without need for potentiallyharmful chemicals such as monomers and initiators.[41]

Photo-polymerization

In situ photo-polymerization has been used in biomedical applications for over more than decade. A solution of monomers or reactive macromere and initiator 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. Photopolymerizable systems when introduced to the desired site via injection get photocured *in situ* with the help of fiber optic cables and then release thedrug for prolonged period of time. A photo-polymerizable is biodegradable hydrogel as a tissue contacting material and controlled release carrier. [41]

Mucoadhesion

Mucoadhesion is the phenomenon in which a synthetic or natural macromolecule adheres to a biological tissue, which can be either an epithelial surface or the mucus layer covering a tissue and are held together for extended periods of time by interfacial forces. It is a complex phenomenon and several steps have been suggested in mucoadhesive bond formation[42]. The first step is the spreading, wetting and dissolution of mucoadhesive polymer at the interface. The second step is the mechanical or physical entanglement between the polymer and the mucus, resulting in an inter-penetration layer. The next step is the result of chemical interactions, such as covalent and ionic bonds, hydrogen bonding and Van-der Waal's interactions. Hydrogen bonds and hydrophobic interactions are the most desirable on developing mucoadhesive systems, since strong primary bonds (e.g. covalent bonds and ionic bonds) could cause irreversible damage of mucosal surface.

Mechanisms of polymer adherence to mucosal surfaces have not yet been fully understood and five theories have been proposed for the mucoadhesion. It is unlikely that a single, universal theory will account for all types of adhesion observed. These theories include the adsorption, diffusion, wetting, fracture and electronic theories. The 'adsorption theory' states that interfacial chemical bonds are formed upon initial contact between mucosal surface and the mucoadhesive polymer. In the 'diffusion theory', it has been suggested that after initial contact between the mucosal surface and the mucoadhesive polymer, a physically entangled network between the polymer and the mucus is formed. The 'wetting theory' is based on the ability of the polymer to spread on biological surfaces. This theory is generally applicable to liquid bioadhesive systems. The 'fracture theory' is related to the force required for the separation of polymers from the mucus below. According to the 'electronic theory', electron transfer occurs between mucosal surface and the

mucoadhesive polymer as a result of their different electronic properties. Electrostatic interactions with the negatively charged mucin surface contribute to the formation of an intermediate inter-diffusion network[43]

Ideal characteristics of mucoadhesive dosage forms

The ideal characteristics of mucoadhesive dosage forms containing bioadhesive polymers are

1. Localization in specified regions to improve and enhance bioavailability of drugs.
2. Prolonged residence time to permit once daily dosing so that patient compliance can be improved.

Evaluation of in Situgel

Clarity

The clarity of formulated solutions can be determined by visual inspection under black and white background[53].

Viscosity

The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid were determined with different viscometer like Brookfield viscometer, Cone and Plate viscometer[54].

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[53,54].

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[55].

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[56,57].

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[58,59].

Recent Advancements in Nasal Drug Delievery System

A gel is a soft, solid or solid like material consisting of two or more components, one of which is a liquid, present in substantial quantity. Gels do not flow under die influence of their own weight. Reversible gels refer to those that have die capacity to make, break and modify the bonds responsible for holding the network together. Gels that do not have this capability because they are held together are termed as permanent gels.

Although many gels exhibit shear-thinning behavior, they cannot be easily delivered to the nasal cavity using normal droppers and spray devices because nasal cavity is an irregularly shaped space and it has folded structure. Hiesame limitation is applicable to powdered formulations. Liquid drops given by nasal route have a low nasal residence time, which is insufficient for drug absorption and the formulation sometime gets drained in the oral cavity.

Thus it will be advantageous to use a stimulus sensitive gel system that will provide the advantages of free flowing liquid till it reaches the surface of mucous and get converted into gel form when it is in contact with mucosal surface so that it will have improved nasal residence time for effective absorption of drug. This type of system will provide the patient convenience of application of formulation. Also a sustained release formulation of this nature will reduce the frequency of drug administration and will improve patient compliance.

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CONCLUSION

The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding first-pass metabolism. Despite the potential of the nasal route, a number of factors limit the intranasal absorption of drug, especially peptide and protein drugs. These are mucus and epithelial barrier, mucociliary clearance and enzymatic activity. Rapid mucociliary clearance of drug formulations that are deposited in the nasal cavity is thought to be an important factor underlying the low bioavailability of drugs administered intranasally.

Some areas were Improvement is required

Nasal drug delivery is fast emerging field as an alternative route for the administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation, undergo first-

pass hepatic metabolism, are incompletely absorbed in the GIT or produce undesirably slow effects when administered orally. Nasal route circumvents bioavailability issues associated with listed factors and also offers the advantage of controlled drug delivery for extended periods of time. The success of a controlled release product is directly linked to patient compliance which in situ gels can offer. Exploitation of polymeric in situ nasal gels for controlled release of drug provides numerous advantages over conventional dosage forms and can be considered as reliable and non-invasive drug delivery system. Exploration of novel gel triggering mechanisms and use of water-soluble, biodegradable polymers for product development of the in situ nasal gel formulations makes them more acceptable.

1. Improved nasal residence time for effective absorption of drug
2. Sustained release formulation will reduce the frequency of drug administration and will improve patient compliance.
3. 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
4. Designing of thermo reversible gel formulations is suitable for nasal administration of certain drugs.

Increasing the residence time of the drug formulation in the nasal cavity, and hence prolonging the period of contact with the nasal mucosa, may improve drug absorption. The physicochemical properties of the drugs is also an important factor that affects the nasal drug absorption; a number of lipophilic drugs have been shown to be completely or almost completely absorbed from the nasal mucosa. The nasal route of administration will probably have great potential for the future development of peptide preparations and other drugs that otherwise should be administered parenterally.

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