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OVER REVIEW OF NASAL *IN SITU* GELS

P. Jagadeesh*, P. Jyothi, M. Bhargav, T. S. Nazma, M. Neeraja, N. Pushpalatha, T. Sharath Babu, S. Shamshad and B. Yellasivamma

Department of Pharmaceutics, Sri Lakshmi Venkateswara Institute of Pharmaceutical Sciences, Proddatur-516360, Kadapa (dis), Andhra Pradesh.

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***Corresponding Author**
P. Jagadeesh
Department of Pharmaceutics, Sri Lakshmi Venkateswara Institute of Pharmaceutical Sciences, Proddatur-516360, Kadapa (dis), Andhra Pradesh.

ABSTRACT

Oral route is technique which is used over a decades. It is most preferred and universal technique for oral administration of drug in the body, but due to certain limitation such as absorption of drug, drug targeting to particular organ can cause problem for administration through oral route. To conquer these types of problem as well as for improvement of drug safety and efficiency a novel approach is developed for delivery of drug i.e. In-situ Nasal Drug Delivery System. In-situ gel is a process in which solution form before administration in the body, but once administrated, it undergo gelation in-situ, to form gel. Nasal drug delivery is one of alternative viable route of drug delivery is one of alternative and viable route of drug delivery. Nasal route is rich in vasculature and highly permeable. Nasal route is suitable for those drugs whose oral administration is problematic due to gastric irritation. The present review focused on framework of nasal system and criteria required of drug candidate to prepare a gel i.e. In-situ gel. Approaches towards various formulation of in-situ gel with respect to temperature, ph and physiochemical condition. The main role of polymers like Poloxamer, Pectine, Cellulose etc in body, absorption of drug by various methods. Various evaluation parameters which is consider during preparation of in-situ gel.

KEYWORDS: In situ gel, Poloxamer, Pectin, Cellulose etc.

INTRODUCTION

Oral drug delivery is the most advantageous 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. Trans mucosal 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 familiar as a very promising route for delivery of therapeutic compounds. In recent years many drugs have been shown to achieve improved 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 Pre-formulation studies of drug.[3] In the last few years, the nasal route has received a great deal of attention as a suitable 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]

- Rapid drug absorption via highly vascularised 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.

1.1 ANATOMY AND PHYSIOLOGY OF NOSE

Structure of nasal mucosa

Figure No: 1.1 Anatomy and physiology of nose.

The nasal cavity is separated 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. Add 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 cm^2, and is divided into two nasal cavities via the septum. The volume of each cavity is something like 7.5 ml, having a surface area around 75 cm2.[11]

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 largely 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 also serve to prevent drying of the mucosa by trapping moisture.[11, 12]

2. 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 thenasal[13] cavities from the cranial Cavity. The olfactory tissue is often yellow in colour, 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 basalcells.[14,15]

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 not easy 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 ABSOBTION 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 are

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 larger than 1000 Daltons show poor bioavailability.[18]

2. Second mechanism- It involves transport through a lipoidal route known as the Trans cellular Process. It is on their responsible for the transport of lipophilic drugs that show rate.[19] dependency 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 distinct as a liquid Formulation generating a solid or semi-solid 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 perception 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 chain shave 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.[24,22,23]

Advantages of in situ gel

- Prolong drug release.
- Reduced systemic side effect.
- Reduced number of application.
- Ease of administration.
- Reduced frequency of administration, better patient compliance.

Significance 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.[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 bio adhesive 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.[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 situ gel systems.
- pH induced in situ gel 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 situation.

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 hydro gels 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.[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 polyvinyl acetyl di ethyl amino acetate (AEA),Poly methacrilic acid (PMMA), polyethylene glycol (PEG), pseudo latexes etc.[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 occurrence of the mono or divalent cations. The polymer which shows osmotic ally induced Gelation is gellan gum, hyaluronic acid and alginates etc.[32, 33]

3. CHEMICALLY INDUCED IN SITU GEL SYSTEM

The chemical reactions which form in situ gel systems are Ionic cross inking, enzymatic Cross linking and Photo-polymerization.

Ionic cross linking

Certain ion sensitive polysaccharides such as carrageen, Gellan gum (Gel rite), Pectin, Sodium Alginate undergo phase transition in presence of various ions such as K+, Ca2+,Mg2+, Na+**.** These polysaccharides decrease 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.[34, 35]

Enzymatic cross linking

In situ formation catalysed 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.[35]

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 poly merizable 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 fibre optic cables and then release the drug for prolonged period of time. A photo-polymerizable, biodegradable hydro gel as a tissue contacting material and controlled release carrier is reported by Sawhney et al.[33]

Table No: 1.1 various types of gelling systems with examples

S.NO	Gel systems	Examples
1	Temperature induced in situ gel system.	Poloxamer (or) pluronics. Methyl cellulose. HPMC. Ethyl (hydroxyl ethyl) cellulose. Xyloglucan.
2	pH induced in situ gel systems.	Cellulose acetate phthalate (CAP) latex. Carbomer. Polyvinyl acetyl diethyl amino acetate (AEA). Poly methacrilic acid (PMMA). Poly ethylene glycol (PEG). Pseudo latexes.
3	Osmotic ally induced in situ gelling system.	Gellangum. Hyaluronic acid. Alginates.

THERMOREVERSIBLEANDMUCOADHESIVEPOLYMERS USED IN NASAL DELIVERY

1. PLURONIC F-127

A compound which has received considerable attention is the polyoxyethylene/ Polyoxyropylene/polyoxyethylenetriblock co-polymer pluronics F127 (polaxomer 407) the thermo reversible 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 tri block copolymers polyoxyethylene and poly oxy propylene. 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 oxybutylene is substituted for oxy propylene as the hydro probe, which can be tailor made to have the necessary sol-gel transition between ambient and body temperatures to Confer in situ Gelation characteristics.

2. SODIUM ALGINATE

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid(M) and α-L-guluronic acid (G) residues joined by 1, 4-glycosidic linkage. The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form 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 bio active molecules, usually as matrix devices. It consists chiefly of sodium salt of Alginic acid; a pluronics acid composed of β-D-mannuronicacid carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage.[38] 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 form a raft on the surface so reducing acid regurgitation.

3. CHITOSAN

Chitosan [2-amino-2-deoxy-(1→4)-β-d-glucopyranan] is a linear cationic polysaccharide which is obtained by a process of de acetylation from chitin, an abundant structural polysaccharide in shells of crustacean, such as lobsters, shrimps, and crabs. Due to the NH_2Groups' resultant from the de acetylation process, chitosan is insoluble at neutral and alkaline pH. However, it can form water-soluble salts with inorganic and organic acids including Glutamicacid, 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. 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 Nano particulates 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 per technetate 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 Para cellular 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. Chemical and biological properties of chitosan, such as muco adhesion and ability in enhancing nasal absorption, are determined by the types of derivatives, degree of de acetylation 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. Recent studies have shown that only protonated, soluble chitosan can trigger the opening of tight junctions and thereby facilitate the Para cellular transport of hydrophilic mannitol. To Improve the poor water solubility of chitosan; some derivatives were synthesized, such as Tri methyl chitosan. Thanou*et al*. reported that the tri methyl chitosan was soluble and effective on enhancing intra nasal absorption even at neutral pH. N-tri methyl chitosan hydrochlorides are more muco adhesive than unmodified chitosan and show a higher bioavailability in vivo compared with the unmodified chitosan. 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. Compared with viral vectors; this alternative vector markedly reduced the safety risks that

meanwhile result in high trans fectability. Recently, many studies show that nasal immunization with chitosan plus in active vaccine is a potentially effective, easily administered form of vaccination. Bordetella per tussis filamentous hem agglutinin and recombinant per tussis toxin have shown to induce very strong systemic and mucosal immune reactions against the antigens when Intra nasally administrated with chitosan. 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 intra nasally, high IgA titers in nasal washings could be found. This was not observed in mice receiving the antigen through subcutaneous injection.

Various types of drugs and its purpose to prepare as nasal *In situ* gels.

S.NO	DRUG	CATEGORY	PURPOSE
1	Salbutamol sulphate	Bronchodilator agent, Tocolytic agent	Improving the bioavailability.
2	Metoprolol succinate	Anti-arrhythmic agent,	Improving the bioavailability
3	Ondansetron hydrochloride	Anti-emetic drug	Improving the bioavailability
4	Diltizem hydrochloride	Anti-arrhythmic agent, Calcium channel blockers.	Developed controlled kinetic drug release and to minimize the toxic effects.
5	Zolmitriptan	Serotonergic, AstraZeneca.	Improving the bioavailability

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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