IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
August 2015 Vol.:4, Issue:1
© All rights are reserved by B.Senthilnathan et al.

An Outlook on *In-Situ* Mucoadhesive Gel for Nasal Delivery

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

L.Karpagavalli[1], B.Senthilnathan[2]*, A.Maheswaran[3] and N.Narayanan[4]

[1, 2] Associate Professor, Department of Pharmaceutics, Jaya college of paramedical sciences, Jaya College of Pharmacy, Thiruninravur, Tamil Nadu, India.*

[3] Principal, Jaya college of paramedical sciences, Jaya College of Pharmacy, Thiruninravur, Tamil Nadu, India.

[4] Research Director (Post graduate studies), Jaya college of paramedical sciences, Jaya College of Pharmacy, Thiruninravur, Tamil Nadu, India.

Submitted: 26 July 2015
Accepted: 1 August 2015
Published: 25 August 2015

HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: *In-situ* gel, nasal mucosa, novel dosage form, first pass metabolism

ABSTRACT

The review was carried out to discuss in detail about the *in-situ* gel nasal drug delivery system as these system have better systemic bioavailability through nasal route as compared to oral route of administration. *In-situ* gel is a novel dosage form for nasal delivery of various drugs. It is infusing into the nasal cavity as low viscous solution and after sometime it forms gel when it contact with the nasal mucosa. The main advantage of using nasal delivery is avoidance of first pass metabolism, high permeability of some drugs in nasal epithelium, quick drug absorption across this membrane, rapid onset of action, improved patient compliance and comfort, sustained and prolonged action in comparison to other drug delivery systems. The formation of gel depends on factors like temperature modulation, pH change, presence of ions, ultra violet irradiation, polymorphism, dissolution rate, solubility, viscosity and osmolarity. The review was focused on anatomy and physiology of nose, advantages, disadvantages, mechanism of drug delivery to the nose, types of dosage form for nasal delivery, barriers in nasal drug delivery, factors influencing nasal absorption, mucoadhesive polymer used in nasal drug delivery system and evaluation of *in-situ* gel nasal drug delivery system.

INTRODUCTION

The most commonly used route of administration for systemic effect is oral administration. But for some drug the systemic effect was not in desirable condition due to oral bioavailability and promoted for the search of more effective route for systemic delivery[1]. Usually the nasal cavity is used for the treatment of local diseases they are rhinitis, migraine, cold, pain and nasal congestion. In recent years it has been proved that many drugs achieved better systemic bioavailability through nasal route[2]. The various formulations used by nasal route are nasal gel, spray, powders, etc. 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]. This is due to the anatomy and physiology of nasal passage that is porous endothelial membrane, large surface area, high total blood flow, the avoidance of first pass metabolism and readily accessibility[3][4]. *In-situ* is a Latin term which means 'In its original place or in position'. *In-situ* gel is a type of dosage form in which the medicament is in solution form before administration into the body, after administered it undergoes gelation to form a gel[5]. Due to its accessibility, nasal drug administration is considered as an alternative route for systemic circulation instead of intravenous administration[6].

Nasal drug delivery also provides a way to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly[7]. The nasal route is an attractive not only for delivery of vaccines due to large surface area and low proteolytic activity but also it improves the patient compliance and decrease the production cost compared to parenteral production[8]. Due to their high permeability the nasal route show only smaller molecular weight drugs the absorption will be more. For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane so the drugs cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier[9]. Penetration enhancers such as surfactants, bile salts and phospholipids increases the drug penetration but in site of clinical use the toxicity test proved that the permeation enhancers has some limitation due their irreversible damage[10,11]. Even though the number of challenges for the researchers to overcome some disadvantages in conventional nasal products and to make effort for the new nasal formulation.

Anatomy and physiology of Nose

The nose is divided into two cavities by presence of septum between them and it extends posterior to the nasal pharynx. The surface area of nasal is about 150 cm^2 and the volume of nasal cavity is approximately 15 ml. Nose has three regions they are vestibular, respiratory and olfactory[12]. The most anterior part of the nasal cavity is vestibule; it opens through the nostril breathing and olfactory plays a major role of human nose in transportation of drugs to the brain. But for systemic drug delivery the respiratory region is important[13]. The respiratory epithelium consists of basal cells, mucus containing goblet cells, ciliated columnar and non-ciliated columnar cells. These cells facilitate active transport processes such as exchange of water, ions between the cells and cilia motility[14]. The cilia are a hair like microvilli which is 300 in numbers. They provide large surface area for the drug absorption and the movement of cilia is like a wave and it helps to transport the particles to the pharynx for ingestion. Below the epithelium the blood vessels, nerves, serous glands, secretory glands are found. There is a presence of capillaries network which is responsible for drug absorption. The epithelium covered by a mucus layer is renewed every 10 to 15 minutes. The pH of the mucus secretion ranges from 5.5 to 6.5 and for children it ranges from 5.0 to 6.7. The mucus layer entrapped the particles which are cleaned by the cilia and they cleared within 20 minutes[15].

Advantages of nasal drug delivery[16] [17]

- Rapid drug absorption
- Non-invasive
- Easy administration
- Good bioavailability
- Improved patient compliance and convenience.
- Large surface area for drug absorption
- Rapid action
- Less side effects
- The nasal drug is used when the drug which are not suitable for oral route.
- Crosses blood brain barrier.
- First pass metabolism is avoided.

Disadvantages for nasal drug delivery

- Removal of drug is not possible in nasal cavity.
- Less number of drugs are given by nasal route.
- Nasal irritant drugs are not given through this route.
- Less than 25-200 µl volume of drugs given by this route.
- Lower molecular weight drugs are only given by this route.
- Frequently use of this route causes mucosal damage.
- The drug absorption may cause allergic problems.
- The reached amount of drug may vary in different regions (brain, spinal cord).

Mechanism of nasal drug delivery

The first step involved in the absorption of drug in nasal cavity is crossing the mucus membrane, because small, uncharged particles were passing through the mucus easily. But charged large molecule does not pass easily through the mucus membrane. The protein present in the mucus layer is Mucin, which binds with the solutes that delays the diffusion and structural changes in the mucus layer are also possible because of environmental changes (i.e. pH, temperature, etc.) [18].

During the drug passage in mucus there are several mechanisms for absorption across the mucosa thus includes simple diffusion, Para cellular transport between cell and transcytosis by vesicle carriers. The restrictions to the drug absorption are essential for metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

The first mechanism is known as paracellular route which involves an aqueous route for transportation. This is slow and passive route. There is log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The drugs with a molecular weight greater than 1000 Daltons are having poor bioavailability[19].

The second mechanism is known as transcellular route which involves transportation through the lipoid route and it is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. The drugs cross the cell membrane by active transport through carrier mediated or opening of tight junctions[20].

Types of dosage form for nasal delivery

The type of dosage form which is used to deliver the formulation into the nose is important by determining the nasal absorption profiles of drugs. The selection of dosage form depends on the drug indication, development and patient population for different nasal dosage form that includes: nasal drops[21], nasal powders, nasal sprays (solutions, suspensions)[22], nasal gels, specialized system (liposomes, microspheres, etc.)[23], nanoparticles, nasal inserts, micro emulsions, and hydrogels [24].

Barriers for nasal drug delivery

Low Bioavailability

The most important factor for limiting the drug absorption in the nasal cavity is polar drugs especially large molecular weight polar drugs such as peptides and proteins have low membrane permeability because bioavailability of polar drugs is usually low about 10% for low molecular weight drugs and not above 1% for peptides (calcitonin and insulin)[25]. The large peptides and proteins are able to pass the nasal membrane using an endocytosis transport process for lower amounts only.

Mucociliary Clearance

The drug administered in the nasal cavity is allowed for fast clearance from the nasal cavity because of mucociliary clearance. This leads to decrease the transport of drug across the nasal mucosa especially when the drug is not absorbed across the nasal mucosa. It has been shown for both liquid and powder formulations because which are not bioadhesive, the half life for clearance is of the order of 15-30 min and it can be overcome by adding bioadhesive excipients in the formulations which gives rapid mucociliary clearance[26]. The clearance may also be reduced by depositing the formulations in the anterior and less ciliated part of the nasal cavity thus leading to improved absorption [27].

Enzymatic Degradation

The low bioavailability of peptides and proteins across the nasal mucosa is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity during passage through the epithelial barrier. Both these sites contain exopeptidases such as mono and diamino peptidases that cleave the peptides on their N and C termini and endopeptidases such

as serine and cysteine, which can attack internal bonds. The enzyme inhibitors of enzyme are used to overcome this barrier [28].

Factors influencing Nasal Drug Absorption [29]

1. Molecular weight

The permeation of the drug (less then 300 Daltons) may affect the drug absorption because it is insignificantly influenced by the physicochemical properties of the drug.

2. Chemical form

Chemical form may affected by the conversions of the drug into salt or ester form.

3. Polymorphism

Absorption is affected by polymorphism which in turn affects the dissolution rate and solubility of drugs through biological membranes.

4. Solubility and Dissolution rate

Solubility and dissolution rate are important parameters for drug absorption. For better absorption drug should get dissolved. If dissolution rate of drug is good then absorption of drug is better.

5. Lipophilicity

If lipophilicity of drug goes on increasing, it increases permeation.

6. pH

The pH of the formulation as well as the nasal surface can affect drug permeation. pH of the nasal formulation should be adjusted in the range of 4.5 - 6.5 to avoid irritation.

7. Osmolarity

Optimum osmolarity should be maintained because it causes shrinkage of the nasal epithelial mucosa and alters the permeation of drugs.

8. Viscosity

Higher viscosity of formulation affect the permeation time by increasing the contact time between the drug and nasal mucosa.

9. Drug concentration, Dose and Dose Volume

Drug concentration, dose and volume of administration are three interrelated parameters which affect the nasal delivery performance.

10. Effect of Deposition on Absorption

Nasal residence time is increased if the formulation is deposited in the anterior portion of the nose and provides longer nasal residence time. The anterior portion of the nose is an area of low permeability while posterior portion of the nose is having higher drug permeability in general, thus providing shorter residence time.

11. Nasal blood flow

Nasal mucosa membrane is very much rich in vasculature. Drug absorption in nasal mucosal membrane is dependent on the vasoconstriction and vasodilation of the blood vessels. It plays a vital role in the thermal regulation and humidification of the inhaled air.

12. Effect of Enzymatic activity

The presences of enzyme proteases present in the nasal mucosa are subjected for the degradation of proteins, peptides and amino-peptidase at the mucosal membrane which affect the stability of drugs.

In-situ gel

In situ is a Latin word which means in position. It is defined as a liquid formulation generating a solid or a semisolid depot after administration[30]. *In situ* gel forming system are those which are when exposed to physiological condition will shift into a gel phase. This new concept was suggested for the first time in the early 1980s. Gel formation occurs through the cross linking of polymer chains that can be achieved by covalent bond formation or non covalent bond formation. Both natural and synthetic polymers were used in the formation of *in situ* gels. *In situ* gel systems are capable of producing sustained release relatively constant plasma profiles [31].

Advantages of *in situ* gel[31]

- Prolong drug release.
- Easy to administer

- Less frequency of administration
- Less systemic side effects
- Reduced number of application.

Principle involved in *in-situ* gelling

The principle involved in *in-situ* gelling of nasal formulation is that the nasal fluid is absorbed by the nasal formulation after administration and forms gel in the nasal cavity. The formation of nasal gel avoids the foreign body sensation. The bioadhesive properties of the gels are used for maintaining contact between gel and mucosa. It acts as release controlling matrix and acts as sustained delivery system. Cilia present backwards help to remove the obstacle if there is any interference present in the propulsion phase. After the formation of gel, dissolution and mucociliary removal occurs. So there is no need to remove the dosage form after it has been depleted of drug [32].

***In-situ* gel formulation**

There are many mechanisms for formulating *in-situ* gels are discussed as follows:

Stimuli response *in situ* gelling system

Thermally triggered system

Under this mechanism, *in-situ* gel is formed by using polymer that changes from solution to gel by changing physiological temperature of the body. When the temperature increases the biomaterials used to form *in-situ* gel leads to transition from sol to gel and produce *in-situ* gel [33].

pH triggered systems

In-situ gel is also prepared by changing pH of the gel based on physiological stimuli and here pH sensitive polymers were used. If the polymer contains weakly acidic groups the swelling of hydro gel increases as the external pH increases but it decreases if the polymer contains weakly basic groups [34].

Osmotically induced *in situ* gelling system

In this method, gelling of the instilled solution is triggered by change in the ionic strength. The rate of gelation is depends on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence as the mono or divalent cations. The polymers are induced gelation are gellan gum, hyaluronic acid and alginates etc.[35].

Chemically induced *in situ* gel system

Ionic cross linking

Some ion sensitive to polysaccharides such as carrageenan, Gellan gum, pectin, sodium alginate undergo phase transition in the presence of various ions such as K^+, Ca^{2+}, Mg^{2+}, Na^+. These polysaccharides fall into the class of ion-sensitive ones [36].

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 physiological conditions without need for potentially harmful chemicals such as monomers and initiators[36].

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 photo cured *in situ* with the help of fiber optic cables and then release the drug for prolonged period of time [37].

Mucoadhesive polymer used in nasal drug delivery system

These polymers make an adhesive force between formulation and nasal mucosa, and therefore improve the retention time of the drug in the nasal cavity. Due to the bioadhesion there is a decrease in the mucociliary clearance of formulation.

1. Cellulose derivative

There are many cellulose derivatives are widely used in different administration routes and most of the cellulose derivatives proved to be effective on enhancing the nasal absorption of drugs in that the soluble cellulose derivatives including hydroxypropyl methylcellulose, hydroxypropyl cellulose (HPC), methylcellulose (MC), and carboxymethyl cellulose (CMC), and insoluble cellulose derivatives such as ethyl cellulose and microcrystalline cellulose (MCC) [38].

Cellulose derivatives can prolong the residence time of drugs in the nasal cavity due to their mucoadhesive properties. It is used as an absorption enhancer which improves 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 [39].

2. Gellan gum

Gellan gum is secreted by *Pseudomonas elodea* and it is an anionic deacetylated exocellular polysaccharides. The formation of gel is depends on temperature and cation induced. These formations consist of gellan solution with calcium chloride and sodium citrate complex. In acidic environment of stomach, gellan gum release calcium ions which lead to the gelation of gellan and form *in situ* gel [36].

3. Pluronic F-127

Pluronics are non ionic in nature and these are available as difunctional triblock copolymers. They are made up of a central block of relatively hydrophobic polypropylene oxide and are surrounded by relatively hydrophilic poly ethylene oxide blocks. 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 variability and laboratory synthesis is complicated so it is called transfer reaction which results in the presence of diblock 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 temperature to confer *in situ* gelation characteristics [40].

4. 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. For ophthalmic formulations alginic acid can be chosen as a vehicle, since it exhibits biological properties like biodegradability and no toxicity. 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 bioactive molecules, usually as matrix devices. 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 Ca^{2+} ions is delayed until the preparation reaches the acidic environment of the stomach through complexation of the Ca^{2+} ions with sodium citrate [41].

5. Polyacrylate

Polyacrylates have been used 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 used in nasal drug delivery[41]. Polyacrylates, capable of attaching to mucosal surfaces, so it prolongs the residence time of drugs at the sites of drug absorption, and it is used for sustained release of drugs in nasal formulation, which result in a more stable blood concentration-time curve. The mucoadhesion capability of 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 [42].

6. Chitosan

Chitosan 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 NH_2 group from the deacetylation process, chitosan is insoluble at neutral and alkaline pH. It can form water-soluble salts with inorganic and organic acids including glutamic acid, hydrochloric acid, lactic acid, and acetic acid. It is applied as pharmaceutical excipients in oral, ocular, nasal, implant, parenteral, and transdermal drug delivery because of its low cost, biodegradability, and biocompatibility [43].

7. Carbopol

Carbopol is a pH dependent polymer. At acidic pH carbopol in solution form but at alkaline pH carbopol forms a low viscosity gel. Viscosity of the carbopol solution is imparted when carbopol is used in combination with HPMC and reducing the acidity of the solution. These come under the category of pH-induced *in-situ* precipitating polymeric systems [44].

Evaluation of *In situ* Gel

Clarity

The clarity of formulated solution can be determined by the visual method that is inspection under black and white background [45].

Viscosity

The viscosity and rheological characters of the formulation either in solution or in gel made with artificial tissue fluid which depends on route of administration were determined by different viscometer like Brookfield viscometer, cone and plate viscometer [46].

Brookfield viscometer is used to determine the viscosity of *in situ* gel before and after gelation. Shear rate varies from 1 to 1000/s. about 2 ml of sample is used to apply on the plate and to ensure that the shearing of formulation does not occur. The readings were noted and average of at least three reading is taken as a point.

Gel- strength

This can be evaluated using a Rheometer[47]. Depending on the mechanism of the gelling agent used, from the sol form, a specified amount of gel is prepared in a beaker. This gel containing beaker is raised at a certain rate, 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.

Determination of gelation temperature

The gelation may be defined as that the temperature at which the liquid phase makes a transition to gel. The liquid formulation is kept in a sample tube, immersed in a water bath and heated at a specific temperature and then heated at a specified rate. The samples shall be examined for gelation, which is said to have occurred when the meniscus would no longer

move upon tilting through 90°C[48]. The gel melting temperature is a critical temperature when the gel starts flowing upon tilting through 90°C shall be recorded. Gel Formation is indicated by a lack of movement of meniscus on tilting the tube.

pH of gel

The pH of *in situ* nasal gel is measured by using pH meter [48].

Drug content

Phosphate buffer saline solution is used to dilute *in situ* nasal gel (10 mg) in 100 ml of volumetric flask and then dissolve the gel by shaking. By using Whatman filter paper, *in situ* nasal gel is filtered and pipette out 1 ml of filtrate and dilute to 100 ml with phosphate buffer saline solution at pH 6.4. Spectrophotometrically drug content is estimated by using standard curve [49].

***In vitro* drug release studies**

For the *in situ* gel formulations 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.In the acceptor chamber, 20 ml of phosphate buffer saline (pH 6.4) at 34^0C is added and a mixture of 95 per cent O_2 and 5 per cent CO_2 is bubbled through the system to ensure the oxygenation and agitation. The temperature of the system is maintained at 34^0C. 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 [50].

Determination of Mucoadhesive Strength

Force which is required to detach the gel from nasal mucosa tissue is measured to determine the mucoadhesive strength of *in situ* nasal gel. With the help of two glass slides, a section of sheep nasal mucosa is fixed on each of two slides using thread. On the first slide 50 mg of gel

is placed and then fixing this slide below the height adjustable pan is done, on the other side of the pan another slide with mucosal section is placed in inverted position. Both slides are placed in contact with each other for 2 minutes to ensure the intimate contact between them. The mucoadhesive force is determined from the minimal weight that detaches the mucosal tissue from surface of each formulation.

Detachment stress (dynes/cm^2) = mg/A

Where, m = weight required for detachment in gram,

g= Acceleration due to gravity (980 cm/s^2),

A = Area of mucosa exposed [51]

Histopathological Evaluation of Mucosa

Phosphate buffer (pH 6.8) is used for incubation of histopathological evaluation of tissue for 6 hours and formulation is compared with tissue incubated in diffusion chamber. 10 per cent buffered formalin solution is used to fix tissue and then embedded in paraffin following routine processing. Glass slides are used to cut the sections. Hematoxylin and eosin are used for staining of tissue. Light microscope is used for detecting tissue damage by examining the tissue sections [52].

CONCLUSION

In situ gels nasal drug delivery system offers the primary requirement of a successful controlled release of many drugs which leads to improve patient compliance. Exploitation of polymeric *in situ* gels for controlled release of various drugs provide a number of advantages over conventional dosage forms. Sustained or controlled or prolonged release of the drug, good stability and biocompatibility characteristics make the *in situ* gel nasal drug delivery systems very reliable. Based on the literature review it was found that many number of novel temperature, pH, and ion induced *in situ* forming solutions have been studied. In future if we make use of biodegradable and water soluble polymers for the *in situ* gel formulations, they can make them more acceptable and excellent. Hence it can be concluded that many researches had investigated on *in situ* gel nasal drug delivery system and much more studies are need to be investigated for the further improvement in the nasal drug delivery system.

REFERENCES

1. Ram Chan Dhakar, Sheo Datta Maurya,Vijay K Tilak, Anish k Gupta, A Review On Factor Affecting The Design Of Nasal Drug Delivery System, Int.J.Drug Delivery,2011; Vol-3:194-208.

2. Gavini E, Hegge AB, Rassu G, et al. Nasal administration of carbamazepine using chitosan microspheres: In vitro/invivo studies. Int J Pharm. 2006, 307: 9-15.
3. Arun Kumar Singh, Anita Singh, N.V.Stheeshmadhav, Nasal Cavity ;A Promising Transmucosal Platform For Drug Delivery And Research Approach From Nasal To Brain Targeting ,J.Drug delivery And T, 2012;2(3) : 22-23.
4. Mainardes RM, Cocenza urban MC, Cinto PO, et al. Liposomes and micro / nanoparticles as colloidal carriers for nasal drug delivery. Curr Drug Deliv. 2006, 3: 275-285.
5. Devi DR, Abhirami M, Brindha R, Gomathi S, Vedha HBN. In-situ gelling system potential tool for improving therapeutic effects of drugs. International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(3): 27-30.
6. Suresh S, Bhaskaran S. Nasal drug Delivery: an overview. Ind J Pharm Sci. 2003, 65: 19-25.
7. Wang X, Chi N, Tang X. Preparation of estradiol chitosan nanoparticles for improving nasal absorption and brain targeting. Eur J Pharm Biopharm. 2008, 70: 735-740.
8. Kang ML, Jiang H, Kang SG, et al. Pluronic F127 enhances the effect as an adjuvant of chitosan microspheres in the intranasal delivery of Bordetellabronchiseptica antigens containing dermonecrotoxin. Vaccine. 2007, 25: 4602–4610.
9. Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol. 2001, 53:3-22.
10. Li L, Nandi I, Kim KH. Development of an ethyl laurate based microemulsion for rapid-onset intranasal delivery of diazepam. Int J Pharm. 2002, 237: 77-85.
11. Illum L, Fisher AN, Jabbal-Gill I, et al. Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of polypeptides. Int J Pharm. 2001, 222: 109-119.
12. Mygind N, Anggard A. Anatomy and physiology of the nose pathophysiology alterations in allergic rhinitis. Clin Rev Allergy. 1984, 2: 173-188.
13. ChoudharyRakhi, Goswami Lakshmi, Nasal Route Novelistic Approachfor Targeted Drug Delivery to CNS, I .R.J.Pharmacy, 2013; 4(3):59-62.
14. J.S.Pasun, A.A.Bagada, M.K, Raval, Nasal Drug Delivery-As an Effective Tool for Brain Targeting: A Review, I.J.P.S.A, 2010; 1(2): 43-55.
15. Panchal DR, Patel UL, Bhimani BV, Daslaniya DJ, Patel GV. Nasal in-situ gel: a novel drug delivery system. International Journal for Pharmaceutical Research Scholars.2012; 1(2):457-473
16. RobertO.Williams, David R.Taft, Jason T, Mcconville, Advanced Drug FormulationDesign To Optimize Therapeutic Outcomes, Vol-172:281-301
17. Swamy N G N, Abbas Z. Mucoadhesive in-situ gels as nasal drug delivery systems: an overview. Asian Journal of Pharmaceutical Sciences. 2012; 7 (3): 168-180
18. Kisan R.Jadhav, ManojN.Gambhire, IshaqueM.Shaikh, VilasraoJ.Kadam, Sambaji S. Pisal, Nasal Drug Delivery System-Factor Affecting And Application, Current Drug Therapy, 2007; 2:27-38
19. Rahisuddin, PramodK.Sharma, GarimaGarg, MohdSalim, Review on Nasal Drug Delivery System with Recent Advancement, I.J.P.Pharma.Sci, 2011; 3(2): 1- 5.
20. Shailja Singh, Kanupriya, S.L.Hari Kumar, Intranasal Thermoreversible MucoadhesiveGels: A Review, I.J.P, 2012; 2(3):548-556
21. Patel RS, McGarry GW. Most patients overdose on topical nasal corticosteroid drops: an accurate delivery device is required. J Laryngol Otol. 2001, 115: 633-635.
22. Ishikawa F, Katsura M, Tamai I, Tsuji A. Improved nasal bioavailability of elcatonin by insoluble powder formulation. Int J Pharm. 2001, 224: 105-114.
23. Morath LP. Microspheres as nasal drug delivery systems. Adv Drug Delivery Rev. 1998, 29: 185–94
24. Basavaraj K, Manvi FV, et al. In situ-forming hydrogels for sustained ophthalmic drug delivery. J Control Release. 2007, 122: 119-134
25. Illum L. Nasal drug delivery: new developments and strategies. Drug Discovery Today. 2002, 7: 1184-1189
26. Soane RJ, Frier M, Perkins AC, et al. Evaluation of the clearance characteristics of bioadhesive systems in humans. Int J Pharm. 1999, 178: 55-65
27. Kublik H, Vidgren MT. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev.1998, 29: 157-177

28. Morimoto K, Miyazaki M, Kakemi M. Effects of proteolytic enzyme inhibition on nasal absorption ofsalmon calcitonin in rats. Int J Pharm. 1995, 133: 1-8.
29. Patil PR, Salve VK, Thorat RU, Puranik PK, Khadabadi SS. Modern encroachment and provocation in nasal drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2013; 4(7): 2569-2575.
30. Heli Shah, Meenakshi Patel, In Situ Gelling System: An Insight, Inventi Impact, 2012;(3):143-170
31. Harnish Patel, Priyanka Patel, TusharBrahmbhatt, MayurSuthar, In Situ Gelling System-A Review,J.Chem.Pharm.Res, 2011; 3(6):217-221.
32. Aman Kant, Suchetha Reddy, Shankraiah M.M, Vankatesh.J.S, Nagesh.C, In Situ GellingSystem-An Overview, Pharmacology online, 2011;2: 28-44.
33. Nirmal HB, Bakliwal SR, Pawar SP. In-Situ gel: New trends in Controlled and Sustained Drug Delivery System.International Journal of Pharm Tech Research. 2010, 2: 1398-1408
34. Aikawa K, Mitsutake A, Uda H, et al. Drug release from pH-response polyvinylacetaldiethylaminoacetate hydrogel,and application to nasal delivery. Int J Pharm. 1998, 168: 181-188
35. Kanhaiya.L.Agraval, Naveen Mehta, AshishNamdev, Anil Gupta, In Situ Gel Formulation for Ocular Drug Delivery System-An Overview, A.J.Biomedical and Pharma. Sci, 2011; 1(4):17
36. Amruta B.Kumbhar, AshwiniK.Rokde, P.D, Chaudhari, In Situ Gel Forming Injectable Drug Delivery System, I.J.P.S.R, 2013; 4(2):597-609.
37. Kishor K.Bhalerao, MeghnaS.Kamble, PravinP.Aute, SandeepM.Dange, Rohini P.Chavan, Krunal K. Vadiya, SanketB. Munot, PravinD.Chaudhari, A Short Review On Stomach Specific Floating In Situ Gel, J.Biomed.And Pharm Res2012; 1(3):1-4
38. Saraswat R., Bhan C. S., Gaur A, A Review on Polymers Used In In-Situ Gel DrugDelivery Systems, I.J.P.Inov, 2012; 1(2): 110-118
39. GouravRajria, Arushi Gupta, In Situ Gelling System: A Novel Approach For Ocular DrugDelivery, Am.J.Pharm.Tech.Res, 2012; 2(4): 25-53
40. Tinu T.S, LithaThomar, Anil Kumar B, Polymer Use In Ophthalmic In Situ GellingSystem, Int.J.Pharma.Sci.Res. 2013; 20(1): 176-183
41. M Madan, A Bajaj, S Lewis, N Udupa, JA Baig,In Situ Forming Polymeric Drug DeliverySystems, Indian J Pharm Sci; 2009; 71: 242-51.
42. Parekh Hejal B**,** RishadJivani, Jivani NP, Patel LD, Makwana Ami, SamejaKrunal,NovelIn Situ Polymeric System-A Review, J.of Drug D & T, 2012; 2(5):136-145
43. SuryavansheSarika .S, Kunjawani H.K, Kawade Jayashree. V, Alkunte Mohita A, YadavDattatray. J, Novel Polymeric In Situ Gel for Ophthalmic Drug Delivery System,I.J.R.P.Sci, 2012; 2(1):67-83.
44. Kalia N, Nirmala, Harikumar SL. In-situ gelling system: a review. Journal of Drug Delivery & Therapeutics. 2014; 4(4): 93-103
45. Balasubramanium, J. Kant, S. Pandit, JK. In vitro and in vivo evaluation of the gelrite gellan gum based ocular Delivery system for Indomethacin, Acta Pharm. 2003, 53: 251-261
46. Srividya B, Rita M, Cardoza PD. Sustained ophthalmic delivery of Ofloxacin from a pH triggered in situ gelling systems. J Control Release. 2001, 73: 205-211
47. Miyazaki S, Suisha F, Kawasaki N. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Release. 1998, 56: 75-83
48. Uttarwar S. Formulation and development of in-situ gelling system for nasal administration for an antiemetic drug ondansetron hydrochloride by using pluronics 127p and pluronics 68. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2012; 3(3): 1103-1118
49. Agrawal VA, Pratapwar AS, Chiddarwar AP. Formulation development and evaluation of mucoadhesive in-situ gelling system for nasal administration of metoclopramide hcl. International Journal of Drug Formulation and Research. 2011; 2(3): 240-261
50. Panchal DR, Patel UL, Bhimani BV, Daslaniya DJ, Patel GV. Nasal in-situ gel: a novel drug delivery system. International Journal for Pharmaceutical Research Scholars.2012; 1(2):457-473
51. Gowda DV, Tanuja D, Khan MS, Desai J, Kumar HGS. Formulation and evaluation of in-situ gel of diltiazem hydrochloride for nasal delivery. Scholars Research Library. 2011; 3(1): 371-381
52. Behl CR, Pimplaskar HK, Sileno AP, Demeireles J, Romeo VD. Effects of physicochemical properties and other factors on systemic nasal drug delivery. Advanced Drug Delivery Review. 1998; 29: 89–116