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Mucoadhesive *insitu* nasal gel- A novel approach

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ABSTRACT - *Insitu* gel is a novel dosage form for nasal delivery of various drugs. It is instilled into the nasal cavity as low viscosity solution and then forms gel after coming in contact with the nasal mucosa. It also prolongs the contact time between drug and absorptive sites in the nasal cavity. *Insitu* nasal gel has got importance due to various advantages like rapid drug absorption, rapid onset of action, to avoid first pass metabolism and the drugs which are not suitable by other routes are given by nasal route. This review article contains various factors that influence nasal drug absorption like molecular weight, chemical form, polymorphism, solubility, dissolution rate, lipophilicity, pH, viscosity and osmolarity. Further, this review gives incite for the preparation of *insitu* nasal gel by various methods *viz*., suspension polymerization, polymerization by irradiation, chemically and physically cross linked hydrogels etc. Evaluation of gels for gelation temperature, gelation time, appearance, pH, drug content, *invitro* permeation studies, mucoadhesive strength, viscosity and rheological studies are also discussed. The review also gives hands on information of recent patents applied/granted for this novel drug delivery system.

Keywords: *Insitu* nasal gel, mucoadhesive polymers, cold technique, drug content, *invitro* studies.

Introduction

Nasal drug delivery is an effective route of administration from the ancient days. There are many drugs which give better systemic availability through nasal route. This route becomes an important tool in the treatment of various disorders. [1] In the last few years, it was investigated that the development of *insitu* gel forming systems increased and many patents for their use in various biomedical applications including drug delivery have been reported. [2] *Insitu* is a Latin term which means 'In its original place or in position'. *Insitu* gel is dosage form in which medicament is present in solution form before administration in the body, but once administered, undergo gelation that is *insitu*, to form a gel.[3] These are prepared as alone or in combination with different stimuli like pH change, temperature modulation and solvent exchange. Now a day's, the development of a new drug molecule is an expensive and time consuming process. Hence the safety and efficacy ratio of "old" drugs can be improved by delivering these drugs in a controlled and slow release manner or by targeted delivery which leads to the development of *insitu* gelling nasal drug delivery systems. [4]

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Nasal drug delivery system has recently applied *insitu* gel dosage form. In the nasal cavity nasal *insitu* gels are instilled as low viscosity solutions and when this comes in contact with nasal mucosa, the polymer which is present in it, changes the solution into a gel, so that it can not only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also releases drug slowly and at a constant rate. Therefore, it is especially useful for all the drugs used chronically. [5]

There are different types of smart polymers, mechanisms of gel formation from the sol forms, which are used to form *insitu* polymeric formulations. In early 1970's there were number of natural and synthetic polymers which had been investigated for controlled release formulations. These polymers along with new ones are still used for formulation and development of *insitu* gel forming drug delivery systems. [6]

The drug absorption in nasal cavity is affected by low residence time of drug. Hence, the development of nasal dosage forms has to consider the anatomic and physiologic characteristics of nasal mucosa and more particularly the rapid mucocilliary clearance that limits the time available for drug absorption from the applied dosage form. [7] So, the possible strategy to decrease rapid mucocilliary clearance is the use of mucoadhesive formulations to prolong the residence time at the nasal absorption site and thereby facilitate the uptake of the drug. The limitations of ordinary gels are not easy to administer, low dose accuracy, irritant to nasal mucosa and give gritty feel. [8]

A nasal mucoadhesive *insitu* gel appears very attractive since it is like a fluid prior to nasal administration and can thus easily be administered as a drop allowing accurate drug dosing. *In-situ* gelation can be achieved by using thermo sensitive smart polymers which by sensing nasal temperature forms gel on instillation. [9]
Various researchers have worked on the development of these nasal mucoadhesive *insitu* gels, a few of them are reviewed here under. Mohan, *et al.* (2012) developed a mucoadhesive *in-situ* gel with reduced nasal mucocilliary clearance in order to improve the bioavailability of the antiemetic drug, Metoclopramide Hydrochloride. The *insitu* gelation was conferred *via* the use of the thermo gelling methyl cellulose upon contact with nasal mucosa whereas mucoadhesion and drug release enhancement were modulated *via* the use of sodium alginate and polyethylene glycol polymers respectively. The results showed that the use of mucoadhesive polymer increased the gel viscosity, decreased sol- gel transition temperature and the drug release. When polyethylene glycol was added it counteracted the effect of mucoadhesive polymer as a result the gel consistency decreased, increased sol gel transition and also increase in *invitro* drug diffusion. The *invitro* tests performed for mucoadhesive strength and drug diffusion showed that nasal *insitu* gelling formulations prepared were having good mucoadhesive strength with nearly 100 per cent drug diffusion within four hours. So this study points to the potential of mucoadhesive *insitu* nasal gel in terms of easy to administration, dose accuracy, improved bioavailability and prolonged nasal residence .[10] Nisha, *et al.* (2012) also formulated environment sensitive gel which is a new dosage form which has been applied in nasal drug delivery recently. The environment sensitive nasal *insitu* gel was prepared for the treatment of migraine. The formulation was prepared in such a manner that the final concentration of the drug was 25 mg/ml. [11]
The available information and various aspects related to nasal mucoadhesive *insitu* gels have been clubbed for the handy information to the readers of this review under different subheads, which are as follows:

Anatomy of nose:
Nose has three regions which include the vestibular, respiratory, and olfactory. The septum divides the nose into two nasal cavities. The surface area of nose is about 150 cm^2 and the anatomy of nose is shown in Figure 1. The respiratory region is responsible for systemic drug delivery. Respiratory region consist of goblet cells, basal cells, ciliated and non ciliated columnar cells. The cells of cilia region consist of 300 microvilli which provide large surface area for drug absorption. The movement of cilia follows wave like pattern and this transport the particles to the pharynx for ingestion. The blood vessels, nerves, serous glands and mucus secretary glands are present below the epithelial blood vessels. There is presence of capillaries network which is responsible for drug absorption. Mucus layer covers the nasal passage membrane that is renewed every 10 to 15 minutes. In adults mucosal secretion pH ranges from 5.5 to 6.5 and among children it ranges from 5.5 to 6.7. Particles are entrapped by mucus layer and cilia clear these particles from nasal cavity. Particles are cleared from nose with in every 20 min. [12]

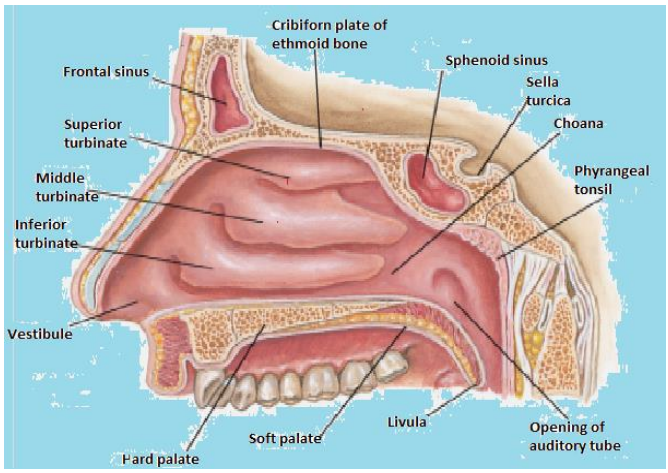

Figure 1: Anatomy of nose

Advantages of nasal drug delivery system [13] [14] [15]

1. Non invasive
2. Self medication is possible
3. Avoid first pass metabolism
4. Rapid drug absorption
5. Pass the blood brain barrier
6. Rapid onset of action
7. Drugs which are not suitable by oral route they are given by nasal route
8. Lower side effects
9. More convenient route
10. Ease of drug administration

Disadvantages of nasal drug delivery system:

1. Removal of drug from nose is not possible
2. There are less number of drugs which are given by nasal route
3. Not more than 25-200 µl volume drugs are given by this route
4. Nasal irritant drugs are not given by this route

5. Large molecular weight drugs are not given by this route
6. Frequent use of this route may cause mucosal damage
7. Drugs reaches in different regions of brain may leads to variation in drug amount
8. Nasal congestion, cold and other allergies may cause problems in drug absorption
9. Drug permeability may alter due to cilliary movement

Mechanism of *insitu* gel formation: [16]

There are many mechanisms by which *insitu* gels are formulated. These mechanisms are discussed as follows:

1. Thermally triggered system–

In this mechanism, *Insitu* gel is formed by the use of polymers that changes from sol-gel by changing physiological temperature of the body. The biomaterials are used to form *insitu* gel. When temperature increases, these biomaterials lead to transitions from sol to gel and form *insitu* gel.

2. pH triggered systems –

Insitu gel is also prepared by changing pH of the gel which is based on physiologic stimuli. All the pH-sensitive polymers are used. Swelling of hydro gel increases as the external pH increases in the case of weakly acidic groups, but decreases if polymer contains weakly basic groups.

3. Swelling -

In this mechanism, *Insitu* gel is prepared when material absorbs water from surroundings and gets swollen.

4. Diffusion-

In this method solidification of polymer matrix occur when diffusion of solvent from polymer solution into surrounding tissue takes place. Example: N-methyl pyrrolidone (NMP) used as a solvent.

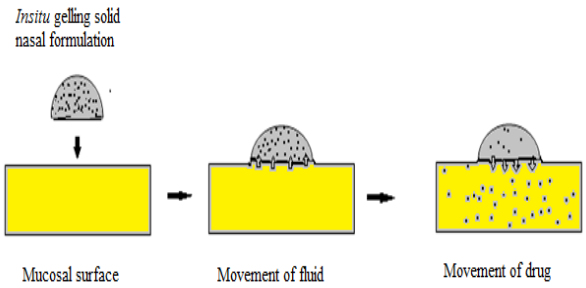

Figure 2: *Insitu* gelling solid nasal formulation

Factors influencing Nasal Drug Absorption: [17]

1. Molecular Weight: The permeation of drugs (less than 300 Dalton) is insignificantly influenced by the physicochemical properties of the drug and may affect the drug absorption.

2. **Chemical Form:** Chemical form play important role in drug absorption. Absorption may be affected by conversions of the drug into a 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 is important parameter of drug absorption. For better absorption drug should get dissolve. 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 that of 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:** Drug absorption in nasal mucosal membrane is dependent on the vasoconstriction and vasodilatation of the blood vessels. Nasal mucosal membrane is very rich in vasculature. It plays a vital role in the thermal regulation and humidification of the inhaled air.

12. **Effect of Enzymatic Activity:** Stability of drugs is affected by the enzymes present in the nasal mucosa. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane.

Principle involved in *insitu* gelling:

The principle of *insitu* gelling of solid nasal formulations is that the nasal formulations absorbs the nasal fluid after administration and forms gel in the nasal cavity. The bioadhesive properties of the gels help in maintaining contact between gel and mucosa and acts as a release controlling matrix system. After the formation of gel, dissolution and mucocilliary removal occurs. Due to this advantage of gel, there is no need to remove the dosage form. [4]

Mucoadhesive polymers:

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 bioadhesion there is a decrease in the mucocilliary clearance of formulation. [11] Mucoadhesive polymers are water soluble and water insoluble polymers. The polymers may have the properties in a manner that they should possess optimal polarity to get sufficiently wetted by the mucus and optimal fluidity to permit the mutual adsorption and interpenetration of polymer and mucus. [2]

Characteristics of mucoadhesive polymers: [18]

1. Should be non toxic
2. It should form a non-covalent bond with the membrane surface
3. It should be non-irritant to the biological membrane
4. It should adhere quickly on the biological membrane
5. The polymer should be stable during the shelf life
6. It should permit incorporation of the drug and allow its release
7. It should be economically low/cheap

Examples of mucoadhesive polymers:

Pectin:

Pectin is a polysaccharide. In the presence of free calcium ions, low methoxy pectin readily form gels in aqueous solution and the galacturonic acid chains are crosslinked. The pectin gelation will occur in the presence of H^+ ions, generally calcium ions are required to produce the gels that act as vehicles for drug delivery**.** Divalent cations leads to the transition of pectin to gel state when administered orally and these divalent cations are generally present in the stomach. Pectin formulations are water soluble. When sodium citrate is added to the pectin solution it forms a complex with most of calcium ions added in the formulation.

Gellan gum:

Gellan gum is secreted by *Pseudomonas elodea* and it is an anionic deacetylated exocellular polysaccharide. It has the capability of gelation which is temperature dependent or cation induced. The formulation consists of gellan solution with calcium chloride and sodium citrate complex. In the acidic environment of the stomach, gellan gum release calcium ions which lead to gelation of gellan and form *insitu* gel. For the oral delivery of theophylline *insitu* gelling, gellan formulation is used as a vehicle.

Xyloglucan:

With the degree of galactose elimination, sol-gel transition temperature varies. On heating up to body temperature it forms thermally reversible gel. Xyloglucan gels are used for various drug delivery systems like oral, intra peritoneal, ocular and rectal drug delivery systems. When its cold solution is administered orally it undergoes slow gelation, resulting *insitu* gelation inside the stomach, therefore allowing its application in oral drug delivery.

Alginic acid:

Alginic acid consists of β-D-mannuronic acid and α-L-glucuronic acid and is a linear block copolymer polysaccharide. On the addition of di and trivalent metal ions, diluted aqueous solutions of alginates form firm gels by a cooperative process. For ophthalmic formulations alginic acid can be chosen as a vehicle, since it exhibit biological properties like biodegradability and no toxicity. Extended pre-corneal dwellings of formulations containing alginic acid provides an extended pre-corneal residence and have the ability to gel in the eye because of its mucoadhesive properties.

Pleuronics:

Poloxamers or pleuronics 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. Due to the PEO/PPO ratio of 2:1, micellar structures above critical micellar concentration are formed when these molecules are immersed into the aqueous solvent. Various grades of pleuronics triblock polymers are available which are differing in molecular weights and physical forms. *Insitu* gels which shows long residence at the application site are prepared by using pluronic F-127 and mucoadhesive polymers like carbopol and HPMC.

Chitosan:
Chitosan is obtained from chitin by alkaline deacetylation and it is thermosenstive, biodegradable and polycationic polymer. Chitin is a natural component of shrimp and crab shell. Chitosan remains dissolved in aqueous solution up to a pH of 6.226 because it is a biocompatible pH dependent cationic polymer. Hydrated gel is formed due to the neutralization of chitosan aqueous solution at a pH exceeding to 6.2.

Carbopol:
Carbopol is a pH dependant polymer. At acidic pH carbopol is present 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 *insitu* precipitating polymeric systems. A pH induced *insitu* precipitating polymeric system (an aqueous solution of carbopol-HPMC system) was designed and developed by Ismail et al. for plasmid DNA delivery. [19]

Method of preparation:

Insitu nasal gel is prepared by using the Cold method described by Schomolka *et al* (1972). Weighed quantity of drug and mucoadhesive polymer like HPMC at different ratios (0.1 %, 0.2 %, 0.3 %, 0.4 %, and 0.5 %) is dissolved in 10 ml of distilled water. Weighed quantity of thermo sensitive polymer, poloxamer 407 (18% w/v), is added slowly with constant stirring to the above formulation and kept at 4^{o} C over night until to form a clear gel. [20]

Other methods of preparation:
A) Solution polymerization/cross linking
B) Suspension polymerization
C) Polymerization by irradiation
D) Chemically cross linked hydrogels
E) Physically cross linked hydrogels

A) Solution Polymerization/Crosslinking
Ionic or neutral monomer and multifunctional crosslinking agents are mixed in the solution for co polymerization reaction. UV light or redox initiator system is used to thermally initiate the polymerization reaction. In the polymerization reaction, solvent serves as a heat link, and decrease problems related to temperature control. Distilled water is used to remove the unreacted monomers, crosslinking agents and initiator which are used to form the hydrogels. By using this method one can synthesize a great variety of *insitu* gels.

B) Suspension Polymerization
Spherical hydrogel micro particles with size range of 1µm to 1mm are prepared by suspension polymerization method. In the non solvent solution, monomer solution is dispersed to form fine droplets and stabilizer is added in this solution to stabilize the fine droplets. Thermal decomposition of free radicals is used to initiate polymerization. Unreacted monomers, crosslinking agents and initiator are removed by washing from prepared microparticles. This method is used to prepare hydrogel microparticles of poly vinyl alcohol.

c) Polymerization by Irradiation
Hydrogels of unsaturated compounds are prepared by using high energy radiation like gamma and electron beams. Radicals on the polymer chain are formed by irradiation of aqueous polymer solution. Covalent bonds are formed by the recombination of the macroparticles on different chains and thus forms a cross linked structure. Polymerization of macroparticles can interact with oxygen during radiation and to avoid it, an inert atmosphere radiation is performed by using nitrogen and argon gas.
Example of polymers crosslinked by radiation method includes poly vinyl alcohol, poly ethylene glycol, and poly acrylic acid.

d) Chemically Crosslinked Hydrogels
Polymers having functional groups like –OH, -COOH, -NH_2, are soluble in water and hydrogels are prepared by forming covalent linkage between the polymer chains and complementary reactivity, such as amine-carboxylic acid due to the presence of functional groups. Hydrogels of polymers containing –OH groups like poly vinyl alcohol are prepared by using gluteraldehyde as a crosslinking agent. Due to the addition reactive functional groups present on the polymer reacts with the crosslinking agent. Unreacted agents have to be extracted because these agents are highly toxic. Organic solvents are used to carry out the reaction and water can react with the crosslinking agent. After formation of hydrogels, drug is loaded on this and released as typically first order release.

e) Physically Crosslinked Hydrogels
Covalent crosslinking agent is known to be toxic. Reversible ionic crosslinking is used to overcome this problem and to form hydrogels. Formation of network

through ionic bridges between the polymeric chains occurs when chitosan reacts with positively charged component like ions or molecules. It is a simple and mild procedure. Auxiliary molecules such as catalysts are not required in contrast to covalent crosslinking. Polyelectrolyte complex with poly acrylic acid can be formed by chitosan. [17]

Patents of *insitu* nasal gel:

Name of topic	Patent no.	Date of filing
Insitu formation of a filler[25]	EP2678049 A1	Feb 17, 2012
Protective gel based on chitosan and oxidized polysaccharide[26]	EP2310002 A1	Apr 23, 2009
Sample preparation for *insitu* nucleic acid analysis[27]	US7964350 B1	May 16, 2008
Delivery of physiological agents with *insitu* gels comprising anionic polysaccharides[28]	CA2537290 C	May 24, 2004
A nasal drug delivery system of ondansetron hydrochloride and process for preparation thereof[29]	209056	Dec 28, 2004
Insitu gel formation of pectin[30]	US20020119941 A1	Feb 28, 2001
Insitu; sustained release; preadministering glucocorticosteroid[31]	US6426339 B1	Apr 3, 2000
Medical uses of *insitu* formed gels[32]	US5958443 A	Dec 23, 1996
Insitu gel for therapeutic use[33]	EP0706372 A1	Jun 1, 1994
Reversible gel-forming composition for sustained delivery of bio-affecting substances, and method of use[34]	US5599534 A	Aug 9, 1994
Compositions and *insitu* methods for forming films on body tissue[35]	US5081158 A	July 28, 1989

Evaluation of *insitu* nasal gel:

Determination of gelation temperature:
The *insitu* nasal gel is evaluated for gelation and gel melting. In the water bath, 2 ml of gel is transferred to the test tube and the temperature is then increased (1^0 C) slowly. Gelation occurs when the meniscus would no longer move upon tilting on 90^o C. [21]

Measurement of Gelation Time:
In a test tube 2 ml of *insitu* nasal gel is taken and kept in an oven at 37^0 C temperature. At particular time gelation of gel is examined. [22]

Appearance
Insitu nasal gel is examined visually for clarity in sol and gel form. [5]

pH of gel
With the help of pH meter pH of *insitu* nasal gel is measured. [21]

Drug content
Phosphate buffer saline solution is used to dilute *insitu* nasal gel (10 mg) in 100 ml of volumetric flask and then dissolve the gel by shaking. By using whatman filter paper, *insitu* 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. [23]

Invitro permeation studies:

For *invitro* permeation studies fresh nasal tissues are used which are carefully removed from the sheep nasal cavity obtained from the local slaughter house. In Franz diffusion cells, tissue samples are inserted. In the acceptor chamber, 20 ml of phosphate buffer saline (pH 6.4) at 34^0 C 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 34^0 C. Formulation and pure drug solution is placed at donor chamber after a pre-incubation time of 20 minutes. From the acceptor compartment, samples are then withdrawn at predetermined time points. After filtering of samples, these are used for analysis. Simultaneously blank samples are taken throughout the experiment to check for any interference. By using suitable analytical technique amount of drug permeated is determined. [12]

Determination of Mucoadhesive Strength:
Force which is required to detach the gel from nasal mucosa tissue is measured to determine the mucoadhesive strength of *insitu* 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 [22]

Stability study:

ICH guidelines are used to perform the stability studies on *insitu* nasal gel. Temperature and humidity conditions of 4^o C ± 2^o C and 60% ± 5% respectively are required to store *insitu* nasal gel for a period of three months and for the studies of color, appearance and pH. [24]

Viscosity and rheological study:

Brookfield rheometer (R/S-CPS +1600) is used to determine the viscosity of *insitu* nasal gel before and after gelation. Shear rate varies from 1 to 1000/s. Spatula is used to apply samples to the plate (approximately 2 ml) and to ensure that shearing of formulation do not occur. Average of at least three readings is taken as a point. [5]

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. [8]

Conclusion

Insitu gel is a novel dosage form for nasal delivery of various drugs which prolongs the contact time between drug and absorptive sites in the nasal cavity. *Insitu* nasal gel has got importance due to various advantages as it has rapid drug absorption, rapid onset of action, avoid first pass metabolism and the drugs which are not suitable by other routes are given by nasal route to prolong the retention time.

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