REVIEW ARTICLE JPAR 2020

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

A review on *in situ* Nasal Gels for Nasal drug delivery system

Mandar J. Bhandwalkar*[1], Imran K Inamdar[1], Shankar B Kalbhare[1], Abhishek D. Changan[1], Supriya N Mandrupkar[2]

[1]Department of Pharmaceutics, YSPM's Yashoda Technical Campus, Satara - 415003, M.S., India.
[2]Krishna Institute of Medical Sciences, Karad, India.

Received: 22.10.2020 Revised: 06.11.2020 Accepted: 12.11.2020 Published: 30.12.2020

ABSTRACT: The oral route is the most favored technique for administering the drug orally in the body. As a result of certain limitations such as drug absorption, poor bioavailability, first-pass hepatic metabolism and drug targeting to particular organs, may cause problems for administration via oral route. Therefore parenteral route, transmucosal route and transdermal route are preferred over oral route. Intranasal route is deemed to be a desirable route because of the time profile of concentration a drug is close to that of the intravenous route. To increase patient safety and efficacy a new approach for drug delivery i.e. *in situ* nasal drug delivery system has been designed. In *in situ* nasal gels drug is administered as a low viscous solution. When in contact with nasal mucosa, the conformation of the polymer changes to gel form. The gel formulation via nasal route is appropriate for those drugs whose oral administration is problematic due to gastric discomfort, drug absorption, poor bioavailability of drug and first-pass hepatic metabolism. For the gel formulation various triggered polymers are used. The present review focused on therapeutic considerations, anatomy and physiology of nasal cavity, challenges and opportunities in nasal drug delivery, marketed products of *in situ* nasal gels and various evaluation parameters considered during preparation of in situ gel.

Corresponding author*
Prof. Mandar J. Bhandwalkar
Head of Department
Department of Pharmaceutics
YSPM's Yashoda Technical Campus
Satara- 415003, M.S., India.
Tel: +91-9028229028
Mail ID:mandar.j.bhandwalkar@gmail.com

Keywords: Nasal Anatomy, Drug delivery, *In situ*, Bioavailability, Transmucosal, Nasal gels.

INTRODUCTION:

Oral drug delivery is a most desirable route for drug administration. Whenever systemic effects are planned out, oral bioavailability of some compounds has promoted the search of more effective route for the systemic delivery [1].To attain faster and higher level of drug absorption nasal mucosa is the major route of administration in Transmucosal route of drug delivery [1]. Transmucosal nasal delivery has been a very promising route of delivery. Many drugs have been shown to achieve better systemic bioavailability through nasal route when compared with the oral route [2]. In the

Ayurvedic systems of Indian medicines, nasal route there is a well-recognized form of treatment; it is known as NASYA KARMA. It is a convenient route for delivery of drugs, which are active in small doses and show minimal oral bioavailability. It is the most suitable dosage form for self-medication [2].

Intranasal administration represents a feasible choice for local and systemic delivery of various therapeutic compounds. The nasal mucosa has a large surface area that affords a quick onset of effects, potential for direct delivery to the central nervous system, it avoids first pass metabolism and shows non-invasiveness; all of this may maximize patient convenience, comfort and compliance [3]. The nasal mucosa acts as a permeation barrier to high molecular weight therapeutic compounds such as proteins and peptides. The tight junctions forming this barrier to paracellular drug delivery can be reversibly and safely opened. Intranasal treatment does not require sterile preparations, it is non-invasive, painless and can also be simply and readily administered by the patient, e.g. in an emergency [4-6].

Intranasal microemulsions, gels and microspheres have increased interest in current years to deliver protein and peptide through nasal route [2]. Recently, *in situ* gel has been introduced as a new dosage form in nasal drug delivery. Liquid nasal formulation compared with *in situ* gels is instilled as low viscosity solutions into the nasal cavity. On interaction with nasal mucosa, the polymer changes its conformation to a gel. So that it not only increases the contact time between drug and absorption site but also slowly releases drugs in the nasal cavity [7].

Therapeutic considerations:

Nose is an integral part of the body for inhalation purposes but when the nose is used as a drug delivery path the effective dose for different drugs has been achieved since the nose provides faster and higher levels of drug absorption and also self-administration possibilities. It is effective in delivery of local, systematic and central nervous system sites [8]. Therapeutic considerations are paramount when selecting the dosing route. These considerations include the pharmaceutical target like local versus systemic, the dosing frequency and the patient population. In approximately cases, intranasal delivery mostly preferred mode of administration [9].

Local delivery:

For the prevention of typical nasal disorder intranasal administration of medications is the natural choice. Common cases are corticoids and antihistamines for cold symptoms. In such a situation, the intranasal route is the principal choice for drug delivery since it shows a rapid sign of relief and shows lesser side effects [8].

Vaccine delivery:

The nasal mucosa was given some antigen through as a route of vaccination. Appropriate antigen with a good adjuvant to the nasal-associated with lymphoid tissue has the ability to encourage humoral and cellular immune responses [10]. This approach may be particularly effective for achieving rapid mass immunization, for instance in children and/or in developing countries and disaster areas [11]. The intranasal immunization can lead to the development of both local and systemic immunity.

Systemic delivery:

The intranasal administration is an effective way of delivering drugs systematically compared to oral and intravascular routes. Thus, the number of drugs administered as nasal formulations intended to attain systemic effects has widely improved [8].

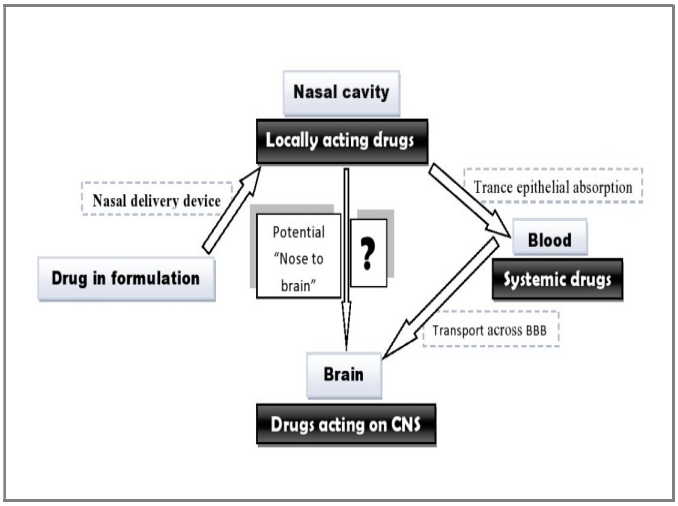

Fig 1. Nose to systemic circulation to brain pathway.

CNS delivery through nasal route:

The tight junctions of Blood Brain Barrier (BBB) surrounding the brain result in a greater trans-endothelial electric resistance (1500 to 2000 Ωcm^2) compared to that other tissues like skin, bladder, colon, lungs (3 to 33 Ωcm^2). The difficulty forced by those brain protective mechanisms has increased the interesting developing strategies to overcome them when brain drug exposure is required. The interpellation imposed by the interesting strategies to overcome them when brain drug exposure is needed for the mechanisms of brain defense has increased. In recent years, intranasal path has occurred

as a positive approach for the delivery of drugs in the brain. The benefits of this drug delivery are the lack of gastrointestinal and hepatic pre-systemic removal [8].

Anatomy and physiology of nasal cavity:

The nasal cavity is divided into two hales by the nasal septum and extends back to the nasopharynx, while the nasal vestibule is the most anterior portion of the nasal cavity, opens up through the nostril to the nose (Fig 2). There are three main regions in the nasal cavity which are the nasal vestibule, the olfactory region and the respiratory region. The surface area in the nose can be increased by the lateral walls of the nasal cavity around 150 cm which contains a folded structure [12]. When compared with its minor volume, its surface area is very high. This folded structure involves three turbinates: the superior, median and the inferior. The nasal airway has narrow passages which is about 1 to 3 mm wide and which helps to perform its principal functions. The nasal cavity is covered by a mucous membrane that splits into two areas; non-olfactory and olfactory epithelium. In the non-olfactory region, the nasal vestibule is lined with skin like stratified squamous epithelial cells, whereas the respiratory field, having a standard airway epithelium filled with multiple microvilli, provides a large area accessible for drug absorption and transportation [13]. In this way, the position of the mucus layer from the anterior to the rare part of the nasal cavity is thus shifted. The mucous membrane protects the nasal turbinate and the atrium. The goblet cells secrete the mucus as mucus granules that swell in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of approximately 95 % water, 2 % mucin, 1 % salts, 1 % of other proteins such as albumin, immunoglobulin, lysozyme and lactoferrin and 1% lipids. The mucous secretion allows immune response suppression of inhaled bacteria and viruses [13].

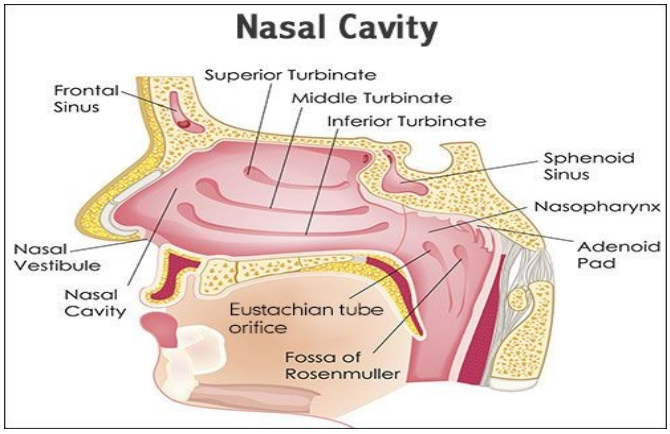

Fig 2. Anatomy of Nasal cavity.

It also performs a number of physiological functions as mentioned below.

- This forms the mucosa, and preserves this physically and enzymatically.
- The mucus has capacity to hold water.
- This exhibits electric behavior on the surface.
- It allows efficient heat transfer.
- It functions as glue and brings particulate matter to the nasopharynx.

Mechanism of drug absorption:

In the first step of absorption, the absorbed drug has to move from the nasal cavity to the mucus layer. Small uncharged drugs can pass through the mucus layer but greater and charged drugs find it very difficult to pass/cross it. Mucin is the main protein of mucus which has a tendency to bind to the solutes and hinders diffusion. The additional structural changes in the mucus layer occur as result of environmental (Temperature and pH) changes.

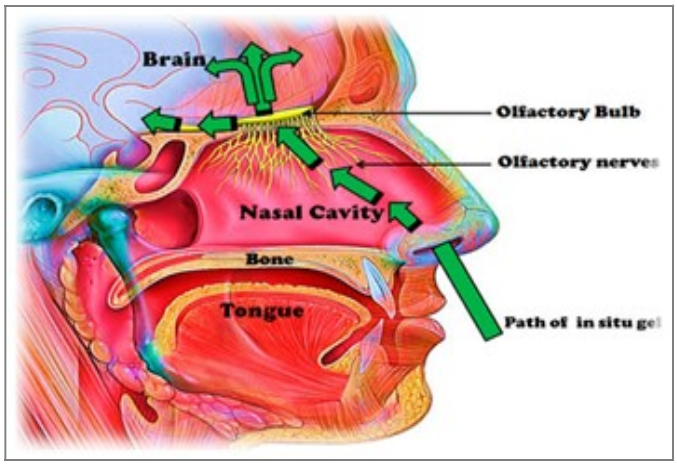

Fig 3A. Position of olfactory bulb with respect to brain and nasal cavity.

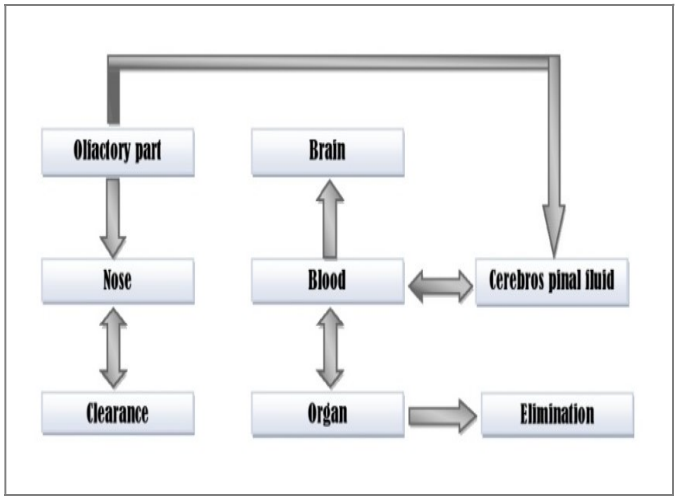

Fig 3B. Different routes to facilitate the drug entry into the brain after intranasal administration.

In this process mainly two mechanisms have been predominantly observed, they are,

- Paracellular transport - It produces aqueous, but sluggish and passive transport route. This route is not appropriate for those drugs that have molecular weight larger than 1000 Dalton due to its poor bioavailability [14].
- Transcellular transport - This develops the lipoidal pathfor lipophilic drug transport [14].

Transport of the drug through the cell membrane can also be brought about by an active transport path. For example, chitosan, a natural biopolymer from shell fish opens tight junctions between epithelial cells to facilitate drug transport [14].

CHALLENGES AND OPPORTUNITIES FOR NASAL DELIVERY SYSTEMS:

The nasal delivery incentives cannot take full advantage of current nasal delivery systems, such as spray, pumps and pipettes. On the frontal section linked by skin a large portion of the dose is deposited and the deposited drug is not targeted for either topical site or systemic circulation. The patient acceptance is decreased because of the bad taste and discomfort to patients caused by drugs brought along the nose floor. Finally, a real task of prolonging nasal administration of drugs and vaccines is inadequate as a result of complex deposition in the remote region with sinus and middle ear openings and in the olfactory region. New advanced and costly drugs require reproducible bioavailability and demanding combination of dependable dosing and high patient compliance to confirm their efficacy and safety. Mostly liquid nasal products are delivered by metered spray pumps [15].

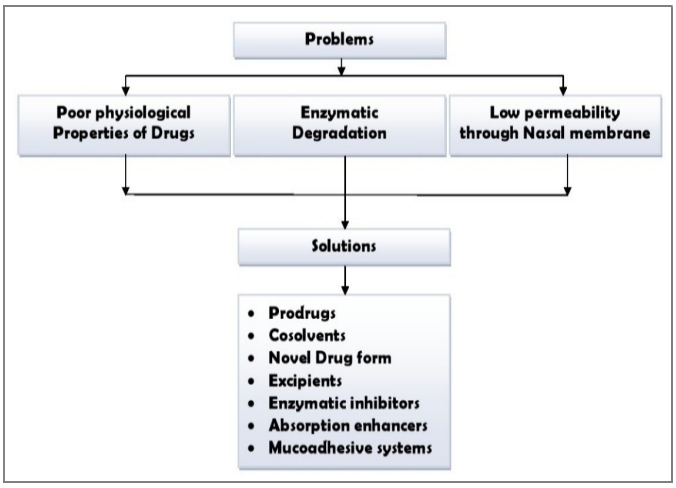

Fig 4. Problems and solutions for *in situ* nasal drug delivery system.

Problems and solutions for in- situ nasal drug delivery system:

The challenges in nasal drug delivery are improved physicochemical properties of drug and formulation, greater permeability and degradation of substances, modify nasal membrane, enhance drug residence time, decrease drug affinity to nasal enzymes, inhibit nasal enzymes, protect nasal enzymes against drug and reduced rapid mucociliary clearance.

CURRENT APPROACHES FOR NASAL PERMEATION ENHANCEMENT:

Based on low drug solubility, rapid enzymatic degradation in the nasal cavity, weak membrane permeation and rapid mucociliary clearance, the bioavailability of nasally administered drugs is largely limited. Several methods to overcome those limitations have been suggested. These methods are enlisted and described below.

Prodrugs:

Lipophilic drugs are poorly water soluble so they easily pass through biomembranes. To make the development of an aqueous nasal formulation probable with an appropriate concentration they should be administered as prodrugs with higher hydrophilic character [16]. The prodrugs must be converted rapidly to the parent drug when in the bloodstream. For example, in contrast with the parent drug many prodrugs of L-Dopa have higher solubility, hence allowing the progress of adequate nasal formulations [15-17].

Co-solvents:

In order to increase drug solubility the usage of co-solvents is an alternative approach for prodrugs. The co-solvents generally used in intranasal formulations include glycerol, ethanol, propylene glycol, polyethylene glycol, and they may be the most relevant as they are non-toxic, pharmaceutically safe, and non-irritating to nasal mucosa [15].

Enzymatic inhibitors:

Nasal mucosa layer serves as an enzymatic barrier during nasal drug delivery, because they have a wide range of enzymes. The different methods are used including protease and peptidase inhibitors to avoid enzymatic degradation. For example, amino peptidases are used as inhibitors in the degradation of calcitonin bestatine, comostate amylase and leupeptin and aprotinin as tyrosine inhibitors probably involved. Furthermore, to help prevent enzymatic degradation of drugs such as

leucine encephalin, bacitracin, amastatin,boroleucin and puromycin has been used [18,19]. Eventually, the enzymatic reduction can also be done by using the absorption enhancers like (bile salts and fluidic acid). Disodium EDTA, an absorption enhancer, has been shown to limit enzymatic degradation of beta-sheet breaker peptide used to treat Alzheimer's disease [20].

Permeation enhancers:

Small and large hydrophilic drugs may exhibit poor permeability across nasal epithelium and may thereby show insufficient bioavailability. The permeation can be improved by administering in combination with absorption enhancers which make reversible changes to the epithelial barrier structure [21]. Permeation enhancers and their mechanism of action with examples are given in Table 1.

METHODS OF FORMULATION OF *IN SITU* NASAL GEL:

Cold method:

In this method of formulation, the product and sample quantity of double distilled water are mixed in a refrigerator and held overnight at 4 ºC. Then the in situ gelling polymer is further added slowly with constant stirring.

In a refrigerator the dispersion is stored till a clear solution is designed and volumes adjusted. When gelling polymers like poloxamer, chitosan or Carbopol are used for formulation then this method is selected. In view of the fact that polymeric dispersion of poloxamer persists as a solution at lower temperatures and is concentrated in gel at higher nasal temperatures because the solubility of poloxamer's propylene oxide chain decreases at high temperatures, resulting in precipitation or salting from polymer.

Likewise, chitosan often requires low temperatures to survive as a solution at room temperature, its hydrophobicity increases with higher temperatures [22].

Hot Method:

This form is preferred if gellan gum or pectin is used as a gelling polymer. Gellan chains dissolve in water at higher temperatures and postulate a random coil conformation with high segmental mobility at high temperatures and proceed as a solution at higher temperatures. In the presence of ions such as K^+ or Ca^{2+} sol-gel transformation occurs when gellan gum solution is cooled. Similarly, pectin also needs a higher temperature for demethoxylation purposes which helps to formulate a solution or dissolve pectin [23].

TRIGGERED *IN SITU* GELLING FORMATION:

Temperature triggered *in situ* gel:

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

Temperature sensitive polymers are the most extensively studied class of environmentally responsive polymer systems in drug delivery. This is because temperature is relatively easy to control and also easily applicable to both *in vitro* and *in vivo*.

In this system, gelling of solution is triggered by alteration in temperature, thus sustaining the drug release.

These hydrogels exist in liquid form at room temperature (20 to 25°C) and undergo gelation when comes in contact with body fluid (35 to 37°C). The use of biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach *in situ* formation. The best critical temperature range for such systems is ambient and physiologic temperature; such that clinical manipulation is facilitated and no external source of heat other than that of the body is required to trigger gelation.

pH triggered *in situ* gel:

Another physiological stimulus that induces formation of *in situ* gel is pH. Polymers included in this class contain an acidic or a basic group that either accept or release protons when they are exposed to different environmental pH. Hence these are called pH sensitive polymers. Most of the pH sensitive polymers containing anionic group are based on PAA (Carbopol®, Carbomer) and its derivatives [7].

Ion- activated *in situ* gel:

In this type of gelation, a polymer that undergoes phase transition in presence of ions. Gellan gum is an anionic polysaccharide that undergoes phase transition in the presence of monovalent and divalent cations like Ca^{2+}, Mg^{2+}, K^+, and Na^+ present in the nasal secretion.

Table 1. Mucosal penetration enhancers and mechanisms of action with examples.

Classification	Examples	Mechanism
Surfactants	Anionic: Sodium lauryl sulphate Cationic: Cetyl pyridinium Chloride. Nonionic: Poloxamer, Span	Intercellular lipid disease, Protein domain integrity, Distorts membrane
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate	Mucolytic activity, Open tight junctions, Distorts membrane
Cyclodextrins	α,β,γ - Cyclodextrin, Methylated β - Cyclodextrins	Inclusion of membrane compounds, Open Tight junctions
Fatty acids	Oleic acid, Methyloleate, Lauric acid, Caprylic acid, Phosphotidylcholine.	Phospholipid fluidity improves domain, Distorts membrane.
Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction on the mucosal surface with negative charge
Chelators	Sodium salicylate, EDTA, Sodium citrate, citric acid	Interfere with CaPolyacrylates
Positive charged polymers	Chitosan, Trimethylchitosan	Ionic interaction with negative chargeon the mucosal surface
Bioadhesive Materials	Carbopol, Chitosan Starch	Opens tight junctions, Reduce nasal clearance

Table 2. Delivery System Based Approaches for Intranasal Drug Delivery.

Formulation	Advantages	Disadvantages
Nasal spray	Nasal sprays may be formulated in the form of solution and suspension Exact dose can be delivered via metered dose pumps and actuators	Less efficient than nasal drops when human serum albumin is stored in the nostrils
Nasal drops	Simple and convenient system	Lack of dose precision
Nasal gels	Due to high viscosity reduction of post nasal drip, reducing the effect of tastes due to reduced swallowing and reduction of anterior formulant leakage	Local side effects
Nasal powders	Absence of preservatives and superior stability.	The appropriateness of powder composition depends on the solubility, particle size, aerodynamic properties and nasal discomfort of active drugs
Liposomes	Active encapsulation of large and small molecules with high hydrophilicity and pKa values	Production cost is high Short half-life
Nanoparticles	Deposits their small size	Only the smallest nanoparticles penetrate to the mucous membrane by paracellular route and in a limited amount

POLYMERS USED FOR THE *IN SITU* GELLING SYSTEM PREPARATION:

Polymer used for pH *In situ* gelling system:

***Carbopol*:**

The water absorption property of Carbopol polymers is very good. Because of the pKa of that polymers is 6.0, they swell in water up to 1000 times its original volume adds 10 times its original diameter to form a gel until exposed to a pH of 4.0 to 6.0. Carbopol polymer has high molecular weight and cross linked polyacrylic acid derivatives and also it has strong mucoadhesive properties. It will reduce polymer concentration and improve concentration and improve gelling property when cellulose addition is done. The mostly used gelling polymers are Carbopol 934 and Carbopol 841 [24].

The Mucoadhesive property is due to electrostatic interaction or hydrophobic interaction, hydrogen bonding. It is an acidic molecule. The carboxylic group within the molecule partially dissociates and forms a spiral when dispersed in water. As it is pH sensitive polymer, a rise in the pH of the solution results in polymer swelling. In two stages the gelling effect is activated, neutralization of result by addition of sodium hydroxide or potassium hydroxide, triethanolamine [24].

Polymer used in temperature sensitive *In situ* gelling system:

***Poloxamer*:**

It is a water soluble tri-block copolymer. It contains two polyethylene oxide and polypropylene oxide in an ABA configuration [25].

It has excellent thermal setting properties and improved drug resistance time and it is also known as Pluronic. It is used as a gelling agent and solubilizing agent. It gives colorless, transparent gel. It is available innumerous molecular weights, having different gelling properties. The gelling property depends upon the ratio and partition of the hydrophobic and hydrophilic chain.

The Poloxamer consists of essential polypropylene oxide enclosed by polyethylene oxide. At room temperature (25 °C), it works as viscous liquid and when temperature increases (37 °C) it transforms to transparent gel. It forms a small micellar subunit in solution at low temperatures and changes in temperature results in increased viscosity resulting in swelling to form a large micellar cross-linking network [26,27].

Polymer used in ion sensitive *In situ* gelling system:

***Sodium alginate*:**

It is extracted from brown algae and it is salt of alginic acid. It is linear block polysaccharides. It consists of two types of monomers β-D-Mannuronic acid and α-L glucuronic acid residues linked by 1,4-glycosidic linkages.It is non-toxic and biodegradable. Due to its carboxylic group it has good mucoadhesive property.

The monomers of alginate β-D-Mannuronic acid and α-L glucuronic acid are arranged as M-M block with altering sequence (M-G) block.G-block polymer interacts with calcium molecules resulting in homogenous gel formation. Mechanical strength and porosity of hydrogel depends on the ratio G: M, type of cross linker used [24].

Synthetic Polymers:

***N-isopropyl acrylamide copolymers*:**

It is a non-biodegradable LCST polymer, which collapses about 32 °C in water and forms cross-linked gels.

***PEG/ PLGA Block copolymers*:**

This is a new concept because they combine thermal gelation, biodegradable, and no toxicity. It was planned for an injectable gel device with greater safety and longer gel length [28].

EVALUATION OF NASAL *IN SITU* GELS [26-32]:

Clarity:

The visual inspection under a black and white backdrop will assess the clarity.

Viscosity:

The viscosity and rheological properties of the polymer formulation can be calculated in solution or gel made from artificial tissue fluid and with various viscometers such as the Brookfield viscometer, cone and plate viscometer.

Texture analysis:

For main indications of the syringe capacity of sol the firmness, uniformity and cohesiveness of formulation may be determined using a texture analyzer so the preparations can easily administer *in-vivo*.

Drug content:

About 1ml of prepared solution is taken in 10ml volumetric flask and made up to 10ml and then diluted with 10ml of distilled water. About 1ml from this solution again diluted up to 10ml with distilled water. Using the UV visible spectroscopy, formulated solutions at specific wavelengths are tested.

Gel strength:

Gel strength can be measured by using a Rheometer. A specific volume of gel is prepared in a beaker. A probe is

pushed through the gel. The changes in the load on the probe can be determined as a function of the depth of immersion of the probe below the gel surface.

Sol-gel transition temperature and gelling time:
The temperature and pH of the sol-gel process should be measured for *in situ* gel forming systems. Gelling time is the time required to detect *in situ* gelling in the first place. The thermosensitive *in situ* gel must be tested for in situ gelling at body temperature.

Drug polymer interaction study and thermal analysis:
By using Fourier Transform Infrared (FTIR) Spectroscopy interaction study may be determined. The technique of employing KBr pellet method the nature of the interacting forces may be measured. The Thermo Gravimetric Analysis (TGA) for *in situ* formation method can be performed to measure the percentage of water in hydro gel. The Differential Scanning Calorimeter (DSC) used to detect some difference in thermo gram compared to the pure active ingredients used for gelation.

Gelling capacity:
Mix *in situ* gel with simulated tear fluid (in the proportion of 25: 7, i.e. application volume 25 µL and volume of tear fluid in eye is 7 µL) to find out the gelling capacity of ophthalmic products. The gelation may be assessed visually by noting the time for and time taken for dissolution of the formed gel.

Sterility testing:
As per the IP 1996 the sterility testing is carried out. In this testing, incubate the formulation in the fluid thioglycollate medium at 30 to 35 ºC for a period of 14 days to find the growth of bacteria and in the soybean casein digest medium at 200 to 25 ºC to find the growth of the fungi in the formulation.

Accelerated stability studies:
In amber colored vials and sealed with aluminum fail the formulation is replaced for the short term. As per ICH state guidelines the accelerated stability done at 40±20 °C and 75±5 % RH.

***In vitro* drug release study:**
In situ preparations to be given by the nasal, ocular, the drug release tests are carried out using the plastic dialysis cell. The cell consists of two half cells containing a donor compartment and a receptor compartment. These are isolated by cellulose membranes. The preparation sol form is put inside the donor container. In an incubator, the assembled cell is then shaken horizontally. The total volume of the receiver solution can be removed at intervals and replaced with the fresh media. This receptor solution is examined using analytical receptor media and placed in a shaker water bath at appropriate temperature and oscillation rate. Samples are routinely removed and examined.

APPLICATION OF *IN SITU* DRUG DELIVERY SYSTEM:

Oral drug delivery system:
The natural polymers including pectin, xyloglucan and gellan gum are used in situ forming oral drug delivery systems. The gelation of pectin usually occurs in the presence of H^+ ions, a source of divalent ions, typically calcium ions are required to produce the gels used as vehicles for drug delivery. The paracetamol was reported as an oral in situ gelling pectin formulation for sustained delivery as possible [33].

Ocular drug delivery system:
The natural polymers such as gellan gum, alginic acid and xyloglucan are mostly used in situ forming oral drug delivery systems. The various compounds such as antimicrobials, anti-inflammatory agents and autonomic drug mostly used to alleviate intraocular stress in glaucoma for this purpose have been used for the local delivery of ophthalmic drugs. Due to the high tear fluids and the complexities, the substances are quickly removed from the eyes. The conventional delivery systems often lead to poor bioavailability and therapeutic reactions. So, bioavailability problems have been identified in ophthalmics in situ gels. Because of the temperature and ionic concentration (Ca^{++}) in the tear fluid, gellan's aqueous solution lowered into the eye undertakes a transition to gel state. In the pharmaceutical application the interest about the gellan gum has focused on its application for ophthalmic drug delivery. The drug release from these in situ gels is delayed due to longer precorneal contact times of the viscous gels compared with conventional eye drops [34].

Nasal drug delivery system
The *in situ* gel device for the nasal delivery of mometasone furoate was developed and tested for its safety and efficacy in the treatment of allergic rhinitis by choosing the nasal route. The polymers such as xanthan gum and gellan gum have been used as *in situ* gel

Table 3. Marketed products of Oral floating *in situ* gels [38].

Drug substances	Brand Name	Indication	Dosage form	Manufacturer
Levodopa, Benserazide	Modapar	Indicated for the prevention of Parkinson's disease	Floating capsule	Roche Products, USA
Diazepam	Valrelease	Indicated to treat management of anxiety disorders	Floating capsule	Hoffmann-LaRoche, USA
Aluminium hydroxide, Magnesium carbonate	Liquid Gaviscon	Indicated to treat the symptoms of too much stomach acid such as stomach upset, heartburn and acid indigestion	Effervescent Floating Liquid Alginate Preparation	Glaxo Smith Kline, INDIA
Aluminium Magnesium antacid	Topsalkan	Indicated for the prevention of relieve heartburn, acid indigestion, and upset stomach	Floating Liquid alginate Preparation	Pierre Fabre Drug, France
Ferrous sulphate	Conviron	Used in the treatment of megaloblastic anemia's, infancy, pregnancy, anemias of nutritional origin etc.	Colloidal gel forming FDDS	Ranbaxy, INDIA
Ciprofloxacin	Cifran OD	Used in the treatment of Pneumonia, Bronchitis, Gonococcal infection, joint infection	G; 2as-generating floating tablets	Ranbaxy, INDIA

Table 4. Marketed products of ophthalmic *in situ* gels [34].

Drug substances	Brand Name	Indication	Dosage form	Manufacturer
Timolol maleate	Timoptic-XE	Indicated in the prevention of raised intraocular pressure in patients with open ocular hypertension or angle glaucoma	Solution	Merck and Co. Inc
Azithro-mycin	Azasite	Indicated for the prevention of bacteria caused by sensitive conjunctivitis isolated of some microorganism i.e. Haemophilus influenza, Staphylococcus aureus, streptococcus mitis group, streptococcus pneumoniae	Solution	In-Site Vision
Lidocaine hydrocloride	Akten TM	Suitable for treating eye surface anesthetics during ophthalmological procedures	Gel	Akten
Ganciclovir	Virgan	Used to treat cytomegalovirus disease in solid organ transplant recipients and in individuals	Gel	Spectrum Thea Pharmaceuticals
Pilocarpine hydrocloride	Pilopine HS	Used to minimize the pressure InSitethe eye and treat dry mouth	Gel	Alcon Lab. Inc.

Table 5. Marketed products of Nasal *in situ* gels [39].

Drug substances	Brand Name	Indication	Dosage form	Manufacturer
Fluconazole	Diflucan	Used to prevent the Antifungal infections	Solution (Spray)	Pfizer Limited, India
Zinc gluconate, Zinc acetate	Zicam	Used to prevent cold and the relief of cold symptoms such as sore throat, runny nose, cough and congestion	Solution (Spray)	Matrixx Initiatives, Inc

Tables 6. Marketed products of Rectal and Vaginal *in situ* gels[40].

Drug substances	Brand Name	Indication	Dosage form	Manufacturer
Diazepam	Diastat	Used to prevent a range of conditions, including alcohol withdrawal syndrome, anxiety, benzodiazepine withdrawal syndrome, seizures, muscle spasms, restless legs syndrome and trouble sleeping	Gel	Valeant Pharmaceuticals
Dinoprostin	Prostin E	Used in labor induction, termination of pregnancy, bleeding after delivery and in newborn babies to keep the duct us arteries open	Suppository	Pfizer Limited, India
Metronidazole	Metrogel Vaginal	Used to prevent certain types of bacterial infections in the vagina	Gel	JM Pharmaceuticals
Progesterone	Crinone	Used to prevent gynecological disorders	Gel	Watson Pharma, Inc.

Table 7. Marketed products of injectable *in situ* gels [41].

Drug substances	Brand Name	Indication	Dosage form	Manufacturer
Ganciclovir	Vitrasert	Used to prevent cytomegalovirus infections	In situ gel	Bausch Health Companies Inc.
Doxycycline	Atridox	Used to prevent adult gum disease (periodontitis)	Gel	DenMat
Leuprolide acetate	Eligard	Used to prevent breast cancer,endometriosis, prostate cancer, uterine fibroids, and primary puberty	Injectable suspension	Tolmar Pharmaceuticals

forming systems. The animal studies were conducted using an allergic rhinitis model and the results of in situ gel on antigen mediated nasal symptoms have been observed in sensitized rats. As compared to marketed nasonex formulation (mometasone furoate suspension 0.05 %) *in situ* gel was found to inhibit the increase in nasal symptoms [35].

Rectal drug delivery system:

It also possesses a potential application for rectal and vaginal drug delivery in situ gels. Miyazaki et al. researched the use of xyloglucan based thermoreversible gels for the rectal drug delivery of indomethacin [19].

Vaginal drug delivery system:

A mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating clotrimazole-β-cyclodextrin complex was prepared for the treatment of vaginitis and gives better therapeutic effectiveness and patient compliance. Pluronic F-127 was used as an *in situ* gel forming polymer with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methyl cellulose to ensure long residence time at the application site [36].

Injectable drug delivery system:

For tumor treatment an injectable, novel, thermosensitive *in situ* gelling hydrogel was developed. It consists of a chitosan solution filled with drugs neutralized with β-glycerophosphate [37].

MARKETED IN SITU GEL FORMULATIONS:

The marketed *in situ* gel formulations are enlisted in Table 3, 4 and 5.

CONCLUSION:

Nasal drug delivery is a novel platform and it is a promising alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the

form of nasal formulation intended for systemic treatment.

Development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetics, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Bioavailability of nasal drug products is one of the major challenges in the nasal product development. In contrast, a huge amount of money is investigated by pharmaceutical companies in the development of nasal products, because of growing demand of nasal drug products in global pharmaceutical market. So for the avoidance of side effect and improve effectiveness of nasal products we should pay attention to basic research.

ACKNOWLEDGEMENT:

The authors are grateful to the authorities of Y.S.P.M.'s Yashoda Technical Campus, Satara for providing the Library facilities to complete this review study.

REFERENCES:

1. Dhakar RC, Maurya SD, Tilak VK, Gupta AK. A review on factors affecting the design of nasal drug delivery system. Int J Drug Deliv, 2011; 1: 194-208.
2. Kushwaha SKS, Keshari RK, Rai AK. Advances in nasal trans-mucosal drug delivery. J Appl Pharm Sci, 2011;1: 21-28.
3. Das P, Gangani A, Maity A. Chromatographic method development approaches and validation for pharmaceutical products. Pharm Methods, 2020; 3: 936-942.
4. Behl CR, PimplaskarHK, Sileno AP, DeMeireles J, Romeo VD. Effects of physicochemical properties and other factors on systemic nasal drug delivery. Adv Drug Deliv Rev, 1998; 29: 89-116.
5. Romeo VD, deMeireles JC, Gries WJ, Xia WJ, Sileno AP, *et al*. Optimization of systemic nasal drug delivery with pharmaceutical excipients. Adv. Drug Deliv. Rev, 1998; 29(1-2): 117–133.
6. Belshe RB. *et al*. Evaluation of Combined Live, Attenuated Respiratory Syncytial Virus and Parainfluenza 3 Virus Vaccines in Infants and Young Children. J Infect Dis, 2004; 190: 2096-2103.
7. Durgapal S,*et al*. Formulation and Evaluation of in situ Nasal Gel of Montelukast Sodium for the Effective Treatment of Asthma. Int J Pharm Sci Res, 2018; 9: 2792-2799.
8. Aishwarya JJ, Sheetal B, Gondkar RBS. A Review on nasal drug delivery system. World J Pharmacy Pharm Sci, 2014;3: 231-254.
9. Bhandwalkar MJ, AvachatAM. Thermoreversible nasal in situ gel of venlafaxine hydrochloride: Formulation, characterization, and pharmacodynamic evaluation. AAPS PharmSciTech, 2014;14: 101-110.
10. Zuercher AW, Coffin SE, Thurnheer MC, Fundova P, Cebra JJ. Nasal-Associated Lymphoid Tissue Is a Mucosal Inductive Site for Virus-Specific Humoral and Cellular Immune Responses. J Immunol, 2002;168: 1796-1803.
11. Roth Y, Chapnik JS, Cole P. Feasibility ofaerosol vaccination in humans. Aan Otol Rhinol Laryngol, 2003; 112(3): 264-270 (2003).
12. Panigrahy UP, Naga Vishnu Kumari K, Ram Mohan Reddy T, Abbulu K. RP-HPLC method development and validation for simultaneous estimation of prazosin and polythiazide in bulk and pharmaceutical dosage form. Res J Pharm Technol, 2020; 13: 1779-1787.
13. Upadhyay S, Parikh A, Joshi P, Upadhyay UM, Chotai NP. Intranasal drug delivery system- A glimpse to become maestro. J Appl Pharm Sci, 2011; 1: 34-44.
14. Kumar GP, Kiran S. Strategies and prospects of nasal drug delivery system. Indian J Pharm Sci Res, 2012; 2: 58-62.
15. Carlfors J, Edsman K, Petersson R, Jornving K. Rheological evaluation of Gelrite® *in situ* gels for ophthalmic use. Eur J Pharm Sci, 1998; 6: 113-119.
16. Munivenkatappa A, Sahay RR, Yadav PD, Viswanathan R, Mourya DT. Clinical & epidemiological significance of Kyasanur forest disease. Indian J Med Res, 2018; 148(2): 145-150.
17. Suisha F,*et al*. Xyloglucan gels as sustained release vehicles for the intraperitoneal administration of mitomycin C. Int J Pharm, 1998;172: 27-32.
18. Chandrashekar G, Udupa N. Biodegradable injectable implant systems for long term drug delivery using poly (lactic-co-glycolic) acid copolymers. J Pharm Pharmacol, 1996; 48: 669-674.
19. Kawasaki N, *et al*. Thermally reversible xyloglucan gels as vehicles for oral drug delivery. Int J Pharm,1999; 181: 227-234.
20. Kashyap N,*et al*. Design and evaluation of

biodegradable, biosensitive in situ gelling system for pulsatile delivery of insulin. Biomaterials, 2007; 28: 2051-2060.
21. Roy N,*et al*. Permeation Enhances: A Major Breakthrough in Drug Delivery Technology. Int J Pharm Sci Res, 2017;8: 1001-1011.
22. Ban MM, Chakote VR., Dhembre GN, Rajguru JR, Joshi DA. *In situ* Gel for Nasal Drug Delivery. Int J Dev Res, 2018; 8(2): 18763-18769.
23. Manashi PV, Sandip AT, *et al*. Review on in situ gel a novel nasal drug delivery system. Int J Pharm Rev Res, 2018; 50: 175-181.
24. Kashid V, Nikam N, Wagh V, Chaudhari S. Nasal Gel as Promising Mucosal Drug Delivery. World J Pharm Res, 5(6); 2016: 891-912.
25. Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. Pharm Res, 2006; 23: 2709-2728.
26. Kakad JK, More PK, Gondkar SB, Saudagar RB. A Recent Review on Nasal Drug Delivery System. Word J Pharm Res, 2014; 4(2): 269-281.
27. Goyal A, Prejapati NB. Thermoreversible Mucoadhesive *In situ* gel: A Review. Int J Innovative Drug Discov, 2013; 3(2): 67-84.
28. Prasad KM., Ravindranath BS, Sheetal BG. Nasal *in situ* gel: A novel approach for nasal drug delivery system. World J Pharm Res, 2015; 4: 686-708.
29. Neha K. Review Article Insitu Gelling System : a Review. J Drug Deliv Ther, 2014; 4(4): 93-103.
30. Yong CS,*et al*. Effect of sodium chloride on the gelation temperature, gel strength and bioadhesive force of poloxamer gels containing diclofenac sodium. Int J Pharm, 2001; 226: 195-205.
31. Patil PR., Salve VK., Thorat RU, Puranik PK, Khadabadi SS. Modern Encroachment and Provocation in Nasal Drug Delivery System. Int J Pharm Sci Res, 2013;4: 2569-2575.
32. Tinu TS, Thomas L, Kumar BA. Polymers used in ophthalmic *in situ* gelling system. Int J Pharm Sci Rev Res, 2013; 20: 176-183.
33. Kubo W, Konno Y, Miyazaki S, Attwood D. *In situ* gelling pectin formulations for oral sustained delivery of paracetamol. Drug Dev Ind Pharm, 2004; 30: 593-599.
34. Majeed A, Khan NA. Ocular *in situ* gel: An overview. J Drug Deliv Ther, 2019;9: 337-347.
35. Cao SL, *et al*.*In situ* gel based on gellan gum as new carrier for nasal administration of mometasone furoate. Int J Pharm, 365: 109-115.
36. Bilensoy E, Rouf MA, Vural I, Sen M, Hıncal AA. Mucoadhesive, Thermosensitive, Prolonged-Release Vaginal Gel for Clotrimazole:β-Cyclodextrin Complex. AAPS PharmSciTech, 2006; 7: 1-7.
37. Chenite A, *et al*. Novel injectable neutral solutions of chitosan form biodegradable gels *in situ*. Biomaterials, 2000; 21: 2155-2161.
38. Bashir R, Majeed A, Ali T, Farooq S, Khan NA. Floating Oral In situ Gel: A Review. J Drug Deliv Ther, 2019; 9: 442-448.
39. Aderibigbe BA. *In situ*-based gels for nose to brain delivery for the treatment of neurological diseases. Pharmaceutics, 2018; 10(2): 40-56.
40. Jannin V, Lemagnen G, Gueroult P, Larrouture D, Tuleu C. Rectal route in the 21st Century to treat children. Adv Drug Deliv Rev, 2014; 73: 34-49.
41. Kumbhar AB, Rakde AK, Chaudhari P. *In situ* gel forming injectable drug delivery system. Int J Pharm Sci Res, 2013;4: 597-609.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Bhandwalkar MJ*, Inamdar IK, Kalbhare SB, Changan AD, Mandrupkar SN. A review on *in situ* Nasal Gels for Nasal drug delivery system. J Pharm Adv Res, 2020; 3(12): 1062-1073.