Available online on 15.04.2024 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

A Novel Approch for Nasal Drug Delivery System

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A B S T R A C T

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 medicine target 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. The nasal route has also been successfully used for bypassing the blood-brain barrier and afterword delivering drug molecules to the central nervous system .The in-situ gelling system is a process in which is in a solution form before the administration in the body but it converts in to a gel form after administration . The formation of gel depends on factors like temperature modulation, pH change, presence of ions from which drug get released in sustained and controlled manner. Therefore this review focuses on nasal drug delivery, a variety of aspects of nasal anatomy and physiology, nasal absorption mechanism, and In-Situ gels evaluations.

Keywords:- Nasal Drug Delivery , In Situ gel , polymers , etc .

A R T I C L E I N F O: Received 10 Nov 2023; Review Complete 10 Mar 2024; Accepted 04 April 2024; Available online, 15 April.2024

Cite this article as:

Avinash J, Dharashive V , Shafi S, Chavan S, Honrao M, Inje R, Biradar A, A Novel Approch for Nasal Drug Delivery System, Asian Journal of Pharmaceutical Research and Development. 2024; 12(2):96-106 DOI: http://dx.doi.org/10.22270/ajprd.v12i2.1383

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INTRODUCTION:

In Ayurveda system of medicine the intranasal treatment is accepted form of treatment. It is also called "NASAYA KARMA". Nasal route has improved systemic bioavailability and it achieves quick and superior level of drug absorption as compared to oral. Nasal route is good because it is more permeable to compounds than gastro intestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of nasal mucus.

In nasal drug delivery formulation, gel formulation is especially famous in pharmaceutical researchers. Gel formulation can stay on any application area more longer time than solution due to the imparted viscosity.

A gel is a state between liquid and solid, which consists of physically cross-linked networks of extended polymer molecules, with liquid molecules trapped within a three-dimensional polymeric network swollen by a solvent. Before administration, the in-situ gelling system is a liquid aqueous solution and it changes into a gel at the physiological state. Prolonged and sustained release of the drug is reproducible, and in-situ gel is biocompatible, with excellent stability and dependable quantities of medication, making it more accurate.

There are a variety of routes for in situ gel medicine delivery, for, example, oral, optical, vaginal, rectal, intravenous, intraperitoneal, etc. Gelation be through crosslinking of the polymer chain, which can be attained through covalent bond formation (chemical crosslinking) or non-covalent bond formation (physical crosslinking). A different medium exists which produce the formation of in-situ gels, like depend on physiologic stimulus (e.g. temperature modifications, pH-triggered systems), those based on physical changes in biomaterials (e.g. Solvent exchange and swelling), and those depend on chemical reaction (e.g. UV radiation, ionic crosslinking and ion activated systems). In this system, there is no need for any organic liquids, copolymerization agents, or a directly

applied stimulate for gelation. In-situ gel expression is carried out for targeted delivery through the vaginal and rectal routes, and the nasal mucosa, circumventing the hepatic first-pass metabolism, which is important for the proteins and peptides delivery that is generally administered via the intravenous route because of their vulnerability to the gastrointestinal protease. (3) (4).

NASAL DRUG DELIVERY SYSTEM

Intranasal delivery mostly offers potentially an alternative viable for various drug delivery. It is appropriate for the local and systemic delivery of different therapeutic compounds. Hence there have been numerous investigations involving the nasal cavity as a feasible site for the administration of many therapeutic agents. It is effective in the treatment of local, systematic and CNS sites.

Local: Intranasal administration of drugs is the natural excellent for the treatment of topical nasal Disease. Among the greatest common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In these cases, the intranasal route is the primary option for drug delivery because it allows a rapid symptom release with less side-effect.

Systemic: The intranasal administration is an actual way to systemically deliver drugs as an alternative to oral and intravascular routes. Consequently, by nasal formulations, the amount of drugs administered intended to achieve systemic effects has widely increased. Approximately prominent examples include analgesics [morphine], cardiovascular drugs as Propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and Ketorolac, and antiviral drugs. (4)

ANATOMY AND PHYSIOLOGY OF NOSE

It is vital to contain a clear understanding of the anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used. In humans and other animal species, the main functions of the nasal cavity are breathing and olfaction. It also affords an significant protective activity once it filters, heat and humidifies the inhaled air before reaching the lowest airways. The human nasal cavity has a total volume of 15-20ml and a entire surface area of approximately 150cm. The nose is separated in 2 nasal cavities by the septum. The capacity of each cavity is about 7.5 ml and has a surface area around 75 cm pH of the mucosal secretions ranges from 5.0 to 6.7 in children and 5.5 to 6.5 in adults. The nasal passage epithelium is covered by a mucus layer that is rehabilitated every 10 to 15 min. From the nose, mucus moves at a rate of 5 to 6 mm/min resulting in particle permission within the nose every 20 min.(4)

Three regions can be distinguished in each part

Respiratory region: The nasal respiratory area is the largest part of the nasal cavity, also called conchae. The respiratory region is the most significant for systemic drug delivery.10-12 The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells. The respiratory region covers three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each of the nasal cavity. For systemic drug delivery, nasal respiratory mucosa is considered the most important section

Vestibular region: Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm this nasal portion is covered by a stratified squamous and keratinized epithelium by sebaceous glands is responsible for filtering out the airborne particles. It is considered to be less significant in the three regions concerning drug absorption.

Olfactory region: The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall it is of about 10 cm2 in surface area and it theatres a vital role in the transportation of drugs to the brain and the CSF. When the drug is administered by the nasal route, it can arrive into the brain by three different paths.

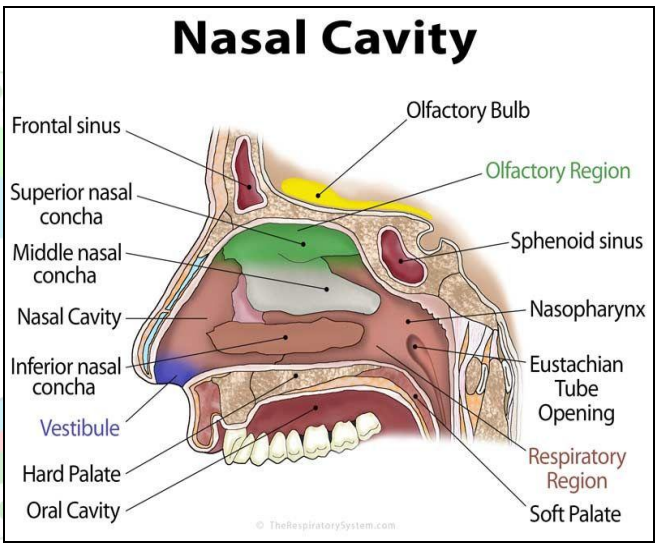

Figure 1: Structure of Nasal Cavity

The primary one is the systemic path, by this route the drug is engrossed into the systemic circulation and subsequently reaches the brain by crossing BBB [especially lipophilic drug]. The other pathways are the olfactory region and the trigeminal neural pathway by which the drug is directly transported from the nasal cavity to CNS [cerebrospinal fluid and brain tissue]. There is a different mechanism by which the drugs across the olfactory membrane reach CNS. The first mechanism includes a direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism be contingent on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The previous one employs pinocytosis by olfactory neurons. (3)

Advantages of Intranasal Drug Delivery System

Table 1: Advantages of Nasal Drug delivery System (9)

Sr . No	Advantages	Factors
1	Improving patient compliance	Needle-free (painless)
2	Good penetration	In case of lipophilic and low molecular weight drugs
3	Rapid absorption and onset of action	Due to relative large surface area high vascularisation
4	Avoidance of the harsh environment	Less chemical and enzymatic degredation
5	Low dose required	Free from first pass effect
6	Direct delivery of drug to central nervous system	Via olfactory region thus bypass the blood brain barrier

Table 2: Limitations of Nasal Drug Delivery System (10)

Sr.No	Limitation	Factors
1	Reduce the capacity of nasal absorption	Due to nasal atrophic rhinitis and severe vasomo rhinitis
2	Risk of local side effect and irreversible damage of cilia on nasal mucosa	Due to constituents added to dosage form
3	Disrupt and even dissolve the nasal membrane	Due to high concentration of absorption enhancer
4	High molecular weight compound cannot be supplied	The volume of 25-200 ml that can be distributed into the nasal cavity is inadequate
5	Irreversible administration	Once the drug administered cannot be removed

Table 3: Structural features of different sections of Nasal Cavity (11) (12)

Region	Structural Features	Permeability
Nasal vestibule	Nasal hairs epithelial cells are stratified squamous and keratinized sebaceous glands present	Last permeable because of the presence of keratinized cells
Atrium	Transepithelial region stratified squamous cells present interiorly and pseudo stratified cells with microvilli present posterior	Less permeable as it has small surface area and stratified cells are present
Respiratory region	Pseudo stratified ciliated columnar cells with microvilli (300 per cell), large surface area receives maximum nasal secretion because of the presence of seromucous gland, nasolacrimal duct and goblet cells	Most permeable region because of large surface area and rich vasculature
Olfactory region	A specialized ciliated olfactory nerve cell for smell perception receives ophthalmic and maxillary division of trigeminal nerve direct access to cerebrospinal fluid	Direct access cerebrospinal fluid
Nasopharynx	Upper part contains ciliated cells and lower part contains squamous epithelium	Receives nasal cavity drainage

BARRIERS FOR NASAL DRUG DELIVERY

Low bioavailability, mucociliary clearance, and enzymatic degradation act as major barriers for nasal drug delivery. a few important characteristics of different barriers which mainly affect the nasal drug delivery are discussed below :

Low bioavailability:

- Bioavailability of polar drugs is fundamentally low (about 10% for low molecular weight drugs and 1% for peptides, for example, calcitonin and insulin).
- Polar drugs have limited nasal absorption with large molecular weight.z
- Drugs can cross the epithelial cell membrane by the transcellular and paracellular routes between cells.
- Polar drugs with a molecular weight below 1000 Da will pass the membrane by the later routes.
- Nasal absorption of polar drugs is enhanced by the co-administration of absorption-enhancing agents.
- Polarity lipophilic:

1. LMW lipophilic -100% bioavailability
2. HMW amphipathic -10% bioavailability
3. Peptides < 1%

Examples

- Surfactants (Sodium lauryl sulfate, sodium dodecyl sulfate, phosphatidylcholines, Laureth-9)
- Bile salts (Sodium glycocholate, sodium taurocholate, sodium deoxycholate)
- Fatty acids and their derivatives (linoleic acid)
- Phospholipids (lysophosphatidylcholine)

- a variety of cyclodextrin and cationic compounds like chitosan, poly-L-arginine, and poly-L-lysine
- Fusidic acid derivatives (sodium tauradihydrofusidate)

Mucociliary clearance:

- It is an important factor that involves in both combine action of mucus and cilia, which fight against inhaled foreign particles in the respiratory tract.
- Drug transport across the nasal mucosa leads to decreases because of high clearance.
- For liquid and powder formulation which are not bioadhesive, the half-life for clearance is of the order of 15-30 min.
- To overcome the quick mucociliary clearance bioadhesive excipients are used in the formulation.
- The clearance may also be decreased by retaining the formulation in the anterior and less ciliated part of the nasal cavity, thus leading to improved absorption.

Enzymatic degradation:

- When peptides and proteins cross the nasal mucosa, there are chances of enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier, which can limit the bioavailability of the medicine.
- These two sites contain exopeptidases such as mono and diamino peptidases that can cleave peptides at their N and C termini, and endopeptidases like serine and cysteine, which can attack internal peptide bonds. The use of enzyme inhibitors, cosolvents, and prodrugs may be the way to overcome this barrier

MECHANISM OF DRUG ABSORPTION

The primary step in the preoccupation of drug from the nasal cavity is passage through the mucus. Small, uncharged particles easily pass through this layer, though large or charged particles may find it more difficult to cross. The principle protein in the mucus is mucin, which has the possible to bind to solutes, hindering diffusion . Structural changes in the mucus layer are likely as a result of environmental changes (i.e. pH, température, etc.) subsequent to a drug's passage through the mucus. Different mechanisms for absorption finished mucosa exist . They comprise transcellular (simple diffusion across the membrane) and paracellular conveyance (movement between cell and transcytosis by vesicle carriers). Drug absorbed can possibly be metabolized before reaching the systemic circulation, and has limited residence time in the cavity . Different devices, such as passive diffusion (transcellular), passive diffusion (paracellular), carrier-mediated transport, transcytosis, absorption, and efflux conveyance have been used for drug transport through the nasal epithelium . Table III discusses about significant comparisons between the two mechanisms, which are extensively used in drug transport through the nasal epithelium. (1) (4) (6)

Table 4: Mechanism of drug passage through the mucus.

First mechanism (Paracellular process)	Second mechanism (Transcellular process)
○ Aqueous route of transport. ○ The process occurs within the cell and transcytosis by vesicle carrier ○ This route is slow-moving and passive ○ It is suited for hydrophilic drugs ○ There is an inverse log-log correlation in between intranasal absorption and the molecular weight of water-soluble compounds ○ Bio-availability of drugs was observed poor with a molecular weight better than 1000 Daltons.	○ Lipoidal route of transport ○ By an active transport route, drugs can also cross the cell membranes with carrier-mediated transport through the openings of tight junctions ○ It is a means of the transport of lipophilic ○ drugs that show a rate-dependency on their lipophilicity ○ For example, chitosan, a natural biopolymer, opens tight junctions between epithelial cells to facilitate drug transport

FACTORS AFFECTING NASAL DRUG DELIVERY SYSTEM

1. Physiochemical properties of a drug

a) **Molecular weight:** Nasal delivery of a is expected to decrease with an increasing molecular weight of the drug molecule. A linear inverse correlation within the absorption of drugs and the molecular weight of the drug has been reported and the molecular weight of the drug is greater than 1000 Da except by using of absorption enhancers. With the use of permeation enhancers, good bioavability to at least 6000 Daltons can be achieved

b) **Chemical form:** It is an important factor for drug absorption. By changing the drug into salt or an ester form can change its absorption; e.g. in situ absorption of carboxylic acid esters of L-tyrosine was meaningfully greater than that of unmodified L-Tyrosine.

c) **Size:** Particle size and morphology of a drug are important tools for the design of nasal drug delivery. Generally, particles in the 5-10 microns range should be deposited in the nostrils. Too fine particles, less than five microns may be inhaled into lungs and should be avoided for nasal products while particles greater then 10μm are deposited with the upper respiratory tract .

d) **Solubility:** Solubility is not only limited the drug absorption, but it can also limit a formulator‟s ability to formulate a formulation if the drug is not sufficiently soluble in the desired vehicles. From a mechanistic and thermodynamic standpoint of view, it is important to learn about the relationship between a drug's saturation solubility and its absorption.

e) **Lipophilicity:** Lipophilic compounds tend to readily cross biological membranes *via* the transcellular route and these compounds can partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Some examples of lipophilic drugs like naloxone, buprenorphine, testosterone, and 17a-ethinylestradiol, are completely or almost totally absorbed by the nasal route in animal models. The permeation of the compound normally increases through nasal mucosa by increasing lipophilicity

f) **Pka and partition coefficient:** According to the pH partition theory, unionized species are absorbed better compared with ionized species and the same holds in the case of nasal absorption.

g) **Polymorphism:** It can affect the rate of drug dissolution, solubility, and absorption through biological membranes (2) (4)

2. Physicochemical properties of a formulation

a) **Drug concentration, dose, and dose-volume:** Drug attentiveness, dose, and dose-volume of administration are three interlinked parameters that affect the performance of the nasal delivery system. If the drug concentration formulation is increasing by increasing formulation volume there may be a limit as to what extent nasal absorption will drain out of the nasal cavity. 0.05-0.15ml is the ideal dose volume with an upper limit of 0.20ml

b) **pH and mucosal irritation:** In addition to the properties of the nasal surface, the pH of the formulation can affect a drug's permeation. Both the pH and pKa of a drug are careful to rationalize systemic absorption. To avoid nasal annoyance, the pH of the nasal formulation should be adjusted to 4.5–6.5. By avoiding nasal irritation results in obtaining an increase in drug permeation and prevents the growth of bacteria. Nasal secretions contain lysozyme, which destroys certain bacteria at acidic pH. Lysozyme is inactivated and the nasal tissue is susceptible to microbial infection under alkaline conditions. (4)

c) **Buffer capacity:** Nasal formulations are administered in little volumes ranging from 25 to 200µL. Hence, nasal secretions may change the pH of the administrated dose. This can affects the attentiveness of unionized drugs available for the absorption. Therefore, an appropriate formulation buffer volume may be required to maintain the pH in-situ.

d) **Solubilizers:** Aqueous solubility of the drug is always a restriction for nasal drug delivery in solution. Co-solvents are used for increasing solubility like glycols, alcohol, Transcutol, medium-chain glycerides and Labrasol can be used to enhance the solubility of drugs.

e) **Preservatives:** Nasal formulations mostly contain preservatives to protect them from microbial contamination. Some generally used preservatives are parabens, benzalkonium chloride, and benzoyl alcohol. Preservatives are used in small amounts and are not likely to affect drug absorption

f) **Antioxidants:** Antioxidants have not any effect on drug absorption or cause nasal irritation. Example-sodium metabisulfite, sodium bisulfate, butylated hydroxyltoluene, and tocopherol.

g) **Humectants:** Intranasal moisture is important for preventing dehydration. Therefore, humectants can be added typically in gel-based nasal products to avoid irritation of the nasal cavity. Humectants do not affect drug absorption. Examples like glycerin, sorbitol, and mannitol.

h) **Absorption enhancer:** Absorption enhancers could also be needed when a drug has poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation. Once a appropriate enhancer is identified, its optimal concentration should be experimentally determined. Generally, higher concentrations of absorption enhancers are probable to result in nasal irritation and damage to the nasal mucosa. On the other hand, inferior enhancer concentrations would generally provide lower or no improvement of absorption.

i) **Osmolarity:** Isotonic solutions are administered for reduction of the nasal epithelial mucosa, because of the effect of osmolarity on the absorption, this results in increased permeation of the compound because of structural changes in the compound. Isotonic solutions also are known to inhibit ciliary activity.

j) **Viscosity:** The advanced viscosity of the formulation upsurges contact time between the drug and therefore the nasal mucosa, thereby increasing permeation time. At the same time, formulations with high viscosity can affect the normal functions like ciliary beating or muco-ciliary clearance and thus changes the permeability of drugs.

3. Physiological factors

a) Blood flow/ supply: Nasal mucosa has a larger surface area and rich with blood supply which makes nasal an optimum place for drug absorption. The blood flow influences significantly the systemic nasal absorption of the medicine so that because it enhances more drug passes through the membrane, reaching the overall circulation**.**

b) Nasal secretion: The mucus layer probably exists as a double layer (5 mm thick) consisting of a periciliary sol phase in which the cilia beat and a superficial blanket of gel are moved forwards by the tip of the cilia. The permeability of drug through the nasal mucosa is suffering from viscosity of nasal secretion. Approximately 1.5-2.1 ml of mucus is produced daily

in the nasal cavity. It is stated that if the sol layer of mucus is too thin, the viscous surface layer will inhibit the ciliary beating, and if the sol layer is too thick, mucociliary clearance is impaired because contact with cilia is lost. The solubility of a drug in nasal secretions: a drug needs to be solubilized before it permeates. Various studies revealed that the secretion ad clearance rates are reduced at night thus altering the permeation of drug. In such cases, chronokinetics will command the pattern and rate of permeation.

c) Nasal cycle: In this process congestion and relaxation regulate the rise and fall in the amount of drug permeation process.

d) A pH of the nasal cavity: Nasal cavity pH in the adult is 5.5-6.5 and 5.0-7.0 in infants. A greater drug permeation is usually achieved at a nasal pH that is lower than the drug‟s p*K*a because under such conditions the penetrant molecules exist as unionized form. A change in the pH of mucus can affect the ionization and thus increase or decrease the permeation of drugs, depending on the nature of the drug. The ideal pH of a formulation should be within 4.5–6.5 and if possible the formulation should also have the buffering capacity.

e) Effect of mucociliary clearance: The main function of the mucociliary clearance system is to remove foreign substances (bacteria, allergens and so on) and particles from the nasal cavity, thus preventing them from reaching the lower airways. Normal mucociliary transit has been reported to be 12 to 15 min. Transit times of more than 30 min are measured to be abnormal and are indicative of impaired mucociliary clearance. Reduced Mucociliary clearance (MCC) and ciliary beating (MCC) increases the time of contact between a drug and the mucous membrane and subsequently enhances drug permeation; whereas, increased MCC decreases drug permeation. Some factors affecting MCC like drugs, hormonal changes of the body, pathological conditions, environmental conditions, and formulation factors.

f) Effect of deposition on absorption: Deposition of the formulation in the anterior portion of the nose provides an extended nasal residence and better absorption, and this is an area of low permeability, whereas, in the posterior portion of the nose, where the drug permeability is generally higher, the deposited drug is eliminated by mucociliary clearance and therefore has a shorter residence time.

g) Effect of enzymatic activity: Many enzymes might affect the stability of drugs that are present on the nasal mucosa. For example, proteins and peptides are subjected to degradation by proteases and aminopeptidases at the mucosal membrane.

4. Biological Factors: Efforts have been made to modify and explore the structural features and mechanism of nasal mucosa to increase its permeability, this is usually not available in the normal physiology of the nasal cavity, mainly during chronic application. These changes could cause unintended adverse effects and result in pathological implications.

a) Structural features: Nasal epithelium mainly consists of different types of cells that show variety in nasal absorption and because of other factors such as presences of microvilli, cell density, surface area, and several cells. The respiratory region is most accurate and suitable for permeation of the compounds.(3)

b) Biochemical changes: A large amount of enzymes such as oxidative and conjugative enzymes, peptidases and proteases are mainly acted on nasal mucus which is an enzymatic barrier for the delivery of drugs. These enzymes are accountable for the degradation of drugs in the nasal mucosa and result in the creation of a pseudo-first-pass effect, which hampers the absorption of drugs. Some example like the nasal P450-dependent monooxygenase system has been implicated in nasal metabolism of nasal decongestants, alcohols, nicotine, and cocaine.

5. Pathological condition: Diseases such as the common cold, rhinitis, atopic rhinitis and nasal polyposis are usually associated with mucociliary dysfunctioning, hypo or hypersecretions, and irritation of the nasal mucosa, which can influence drug permeation.

a) Environmental condition: Temperatures in the range of 24°C cause a moderate reduction in the rate of MCC. A linear increase in ciliary beat frequency occurs with an increase in temperature, which in turn influences the properties of the mucous membrane. (1)

DIFFERENT METHODS TO IMPROVE NASAL ABSORPTION

1. **penetration enhancers:** A variety of penetration enhancers have been investigated to improve the nasal absorption, like fatty acids, bile salts, phospholipids, surfactants, cyclodextrin, etc., which act via different mechanisms such as reserve of enzyme activity, reduction of mucus viscosity, decreasing muco-ciliary clearance, opening tight junctions, and solubilizing or stabilizing the drug.
2. **Prodrug approach:** Prodrugs are the sedentary chemical moiety that becomes active at the target site. This
3. approach is mainly used to improve physicochemical properties such as taste, solubility, and stability of the formulation. This approach includes the derivatization of C and N termini, esters, and cyclic prodrugs
4. **In situ gel:** The conversion into a gel by the influence of stimuli including temperature, pH, and ionic concentration, is possible with substances like Carbopol, cellulose derivatives, lecithin, chitosan, etc. These formulations usually control the problems of administration.
5. **Nasal enzyme inhibitors:** Enzyme inhibitors like protease and peptidase are rummage-sale as inhibitors for the formulation of peptide and protein molecules. Additional examples are bile salts, amastatin, bestatin, boroleucine, fusidic acids, etc.

6. **Structural modification:** Drug structure can be customized without changing the pharmacologic activity, to improve nasal absorption. Chemical modifications are mainly used to modify the physicochemical properties of the drug such that they lead to improved nasal absorption of the drug.
7. **Mucoadhesion:** Mucoadhesion is defined as the position in which two materials are held together for a long period. Mucoadhesive polymers make contact with the biological membrane, and after the establishment of contact, they penetrate the tissue surface. Natural polymers can be easily obtained from natural sources, and require an environmentally- friendly method of processing at a low cost. Some instances include potato starch, rice starch, maize starch, wheat starch, guar gum, tragacanth, xanthan gum, etc. Synthetic polymers have high cost of production and also produce environmental pollution during synthesis. These polymers include polyethylene oxide, polyvinyl alcohol, methylcellulose, ethylcellulose, hydroxyl propylmethylcellulose, etc

IN SITU GEL

In Latin, in situ means 'in position' or 'in its original place'. For the past 30 years, better attention has been directed towards the growth of controlled and sustained drug delivery systems. A vast amount of investigate has been carried out in designing polymeric systems such as in situ gels. In situ gel formation of drug delivery systems can be defined as a liquid Preparation generating a solid or semisolid depot after administration. In situ activated gel, forming Systems are those which are when exposed to physiological conditions that will shift to a gel phase. This new concept of manufacturing a gel in situ was suggested for the first time in the early 1980s. Gelation happens via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or Non-covalent bond formation (physical cross-linking). The ways of administration for in situ gel could be oral, ocular, rectal, vaginal, injectable and intra-peritoneal. (1) (2)

IMPORTANCE OF IN SITU GELLING SYSTEM

The major importance is that the possibility of administering accurate and reproducible quantities compared to already formed gel. It increases the exposure time of drugs with that of mucus at the site of absorption and has better bioavailability, increases patient compliance (1)

PRINCIPLE OF IN SITU GELLING SYSTEM

The principle of in situ gelling system is of solid nasal formulations are that the nasal formulations absorb the nasal fluid after administration and form a gel within the cavity. The foreign body sensation can avoid by the formation of nasal gel within the cavity. Due to bioadhesive nature, the gel adheres to the nasal mucosa. It acts as a release controlling matrix and thus acts as a sustained drug delivery system. In the nose, the mucus lower layer comes and goes around the cilia, forward in the propulsion phase, backward in the preparatory phase. At the propulsion phase, cilia extremity scrapes the upper layer of mucus penetrating it almost 0.5 mm. ciliary activity zones then occur at various intervals. Cilia are situated backward which helps to remove any obstacle if there is any intervention in the propulsion phase. After the formation of the gel, dissolution occurs and or the mucociliary removal to the nasopharynx occurs. Therefore there is no need to remove the dosage form after it has been depleted of a drug.

PROPERTIES OF NASAL IN- SITU GEL

- It should have a long residence time.
- It should be low viscous.
- Free-flowing allows for reproducible administration to the nasal cavity.
- The nasal in-situ gel follows the phase transition mechanism and shear forces in nasal cavity wall (7)

Advantages of In-Situ Gelling System

- improved residence time of drug in nasal cavity.
- Decreased frequency of drug administration.
- Results in rapid absorption and onset of action.
- Avoid degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
- Low dose required.
- Minimized local and systemic circulation and CNS possible.
- Offers minor risk of overdose of CNS acting drugs.

TRIGGERED IN SITU GELLING FORMATION:

Temperature triggered in situ gel:

There are some polymers which experience large and unexpected physical and chemical changes in reply 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 incentive 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.

pH triggered in situ gel:

Another physical stimulus that induces creation 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 (13)

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 Ca2+, Mg2+, K+, and Na+ present in the nasal secretion.

METHODS OF FORMULATION

1. Cold Method:

In this method, the drug is stirred with a sufficient quantity of double distilled water and kept overnight at 4°C in a refrigerator. The in situ gelling polymers are then added slowly with stirring. The dispersion is stored in a refrigerator till a clear solution is formed and finally volume is adjusted with distilled water. This method is selected when poloxamer, chitosan or carbopol is used as a gelling polymer. Considering the fact that polymeric dispersion of poloxamer is in solution at lower temperature and gets converted into a gel at higher nasal temperature because the solubility of polypropylene oxide chain of poloxamer decreases at a high temperature which results in precipitation or salting-out of a polymer. Similarly, chitosan also requires the low temperature to remain as a solution at room temperature, its hydrophobicity increases with an increase in temperature (6)

2. Hot Method:

This method is used when gellan gum or pectin is used as a gelling polymer. At high temperature, gellan chains melt in water and shoulder a random-coil conformation with high segmental mobility at high temperatures and remain as a solution at a higher temperature. A phase transition occurs on a cooling gellan gum solution in the presence of ions like K+ or Ca2+. Similarly, pectin also requires a high temperature for its demethoxylation, which helps in the formation of a solution or dissolving of pectin (6)

POLYMER USED IN IN-SITU GEL :

1. The polymers and their degradation products should be nontoxic and non-absorbable from the gastrointestinal tract.
2. It should stick on quickly to the moist tissue and should possess some site-specificity.
3. It should not irritate the mucous membranes.
4. It should possess a wide safety margin both locally and systemically.
5. The value of the polymer should be not too high so that the prepared quantity form remains Competitive.

Classification of in situ gelling polymers :

Polymers can be categorized based on their origin or the process of gelation. Gelling systems are divided into two categories, according to an on-site source"(15)

- **Natural polymers** (e. g., sodium alginate ,Alginic acid, carrageenan, chitosan, guar gum, gellan gum, pectin, sodium hyaluronate, xanthan gum, xyloglucan, etc.)(16)
- **Synthetic or semi-synthetic polymers** (e. g., Carbopol, CAP, HPMC, MC, PAA, PLGA, poloxamers)(14)

DIFFERENT POLYMERS USED FOR THE PREPARATION OF IN-SITU GELLING SYSTEM:

1. **Polymer used for pH-sensitive In-situ gelling system**

Carbopol: Carbopol shows sol-gel transition in aqueous solutions as the pH is raised above its pKa. The acidic carboxyl groups of the polymer partially dissociate in water and begin to uncoil to produce a flexible coil structure. In acidic circumstances, a small proportion of the carboxyl groups present on the polymer dissociate, producing a flexible coil structure. In an alkaline environment, the carboxyl groups ionize, generating negative charges along the polymer backbone. Electrostatic repulsion of the anionic group causes uncoiling and expansion of the molecule which results in polymer swelling and gel formation. Further addition of carbopol thins the gel because the cations screen the carboxyl groups and so the electrostatic repulsion decreases.

2. **Polymer used for temperature-sensitive In-situ gelling system**

Poloxamer: Poloxamer is a water-soluble tri-block copolymer consisting of two polyethylene oxide and polypropylene oxide core in an ABA configuration. Poloxamer is also known as pluronic. Poloxamer has good thermal setting property and increased residence time of the drug. It performances as a gelling agent and solubilizing agent. Poloxamer gives colorless, transparent gel. Depending on the ratio and distribution of hydrophilic and hydrophobic chain different molecular weights are available and it has different gelling properties. It consists of central polypropylene oxide surrounded by polyethylene oxide. At temperature (25° C), it acts like a viscid liquid and it gets transformed to form a transparent gel when temperature increases (37°C). It forms a small micellar subunit in solution and increases in temperature results increase in viscosity result in swelling to make large micellar cross-linked network at a lower temperature.

Chitosan: Alkaline deacetylation of chitin produces a biodegradable,biocompatible, thermosensitive, pH-dependent, cationic amino polysaccharide. pH and temperature variations cause chitosan to gel. Because of the electrostatic interaction between positively charged chitosan and negatively charged mucosal surfaces, it possesses strong mucoadhesive characteristics. Gels produced with electrostatic forces at low critical solution temperatures due to severe hydrophobic interactions. The gelation process of chitosan is carried out using displaying polymers at temperatures over the critical solution temperature. This is the second most common polysaccharide used after cellulose since it is readily available, non-toxic, and cheap.

Xyloglucan : Xyloglucan is obtained from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. When its partially degraded by β- galactosidase, the obtained product exhibits thermally reversible gelation by the lateral stacking of the rod-like chains. The temperature of phase change sol-gel transition varies with the amount of galactose removal. It forms the thermally reversible gels on warming to body temperature. Xyloglucan has the main request in oral delivery exploits the proposed slow gelation time (several minutes) that might permit in-situ gelation within the stomach following the oral administration of chilled xyloglucan solution. Xyloglucan gels mainly used for oral, intraperitoneal, ocular and rectal drug delivery

3. **Polymer used for ion-sensitive In-situ gelling system**

Sodium alginate: sodium alginate is a salt of alginic acid. It is extracted from brown algae. It has a linear block

polysaccharide containing two type monomers β-D-Mannuronic acid and α-L glucuronic acid residues connected by 1,4 glycosidic linkages. Sodium alginate biodegradable and non-toxic which exhibit good mucoadhesive property due to the presence of the carboxylic group. The mechanism of polymer is 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. Upon interaction of G block of polymer with calcium, moieties give in the formation of a gel. On G: M ratio the mechanical strength and porosity of hydrogel depends, type of crosslinker used and concentration of alginate polymer solution

Gellan gum: Gelrite or Kelcogel is a linear, water-soluble, temperature-dependent, extracellular, hetero, anionic polysaccharide; similar to alginate, this gellan gum gels in the presence of metal cations (mono or divalent). Cross-linking gelation is induced by monovalent cations such as Na+ or K+, as well as divalent cations such as Ca+2 or Mg+2. The gelation process begins with the creation of doublehelical junction zones, which are then followed by the aggregation of the double-helical section into 3-D networks by cation complexation and hydrogen bonding with water. It is one of the most widely utilized polymers in the manufacture of in situ gels

Pectin: Pectins are a family of polysaccharides, in which the backbone of polymer mainly contains α-(1-4)-D-galacturonic acid residues. Low methoxy pectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner described by the egg-box model. Although the gelation of pectin will occur in the presence of H + ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. The main advantage of using pectin for these formulations is that it is water-soluble, so organic solvents are not necessary for the formulation. Divalent cations current in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complex form may be included in the formulation for the induction of pectin gelation.

Xanthum gum: Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic charm of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.

EVALUATION PARAMETERS OF NASAL IN-SITU GELS

1. **Clarity:** The clarity of in situ gel is find out by visual inspection under the black and white background.
2. **Sol-gel transition temperature and gelling time:** For In-Situ gel-forming systems, the sol-gel transition temperature and pH should be determined. Gelling time is the time required for the first detection of gelation of the in-situ gelling system. Thermosensitive in-situ gel should be check for in-situ gelling at body temperature.
3. **Gelling capacity:** Mix in-situ gel by simulated nasal fluid (in the proportion of 25:7 i.e. application volume 25µl and volume of nasal fluid in the nasal is 7 µl) to find out the gelling volume of the ophthalmic product. The gelation may be assessed visually by noticing the time for and time is taken for the dissolution of the formed gel.
4. **Viscosity:** The viscosity and rheological properties of the polymeric formulations, either in solution or in a gel made with artificial tissue fluid and may be determined with different viscometers like Brookfield viscometer, cone, and plate viscometer. The viscosity of these formulations must be such that it should be patient compliance.
5. **Texture analysis:** The firmness, consistency, and cohesiveness of formulation may be determined using a texture analyzer which mainly indicates the syringe ability of sol so the formulation can easily be administered in-vivo.
6. ***In vitro* drug release studies:** For in-situ formulations to be administered by oral, ocular, or intranasally the drug announcement studies are carried out with the plastic dialysis cell. The cell is made up of the two-compartment, a donor compartment and a receptor compartment. Both cells are unglued with the help of the cellulose membrane. The formulation is placed in the donor compartment. The specific volume of the receptor solution can be removed at specific time intervals and replaced with the fresh media. This receptor solution is analyzed for the drug announcement using an analytical method.
7. **Sterility testing:** Sterility testing is approved out as per the IP 1996. Incubate the formulation for not less than 14days at 300˚-350˚C in the fluid thioglycolate medium to find the growth of bacteria and at 200˚-250˚C in soyabean casein digest medium to find the growth of fungi in the formulation.
8. **Accelerated stability studies:** Formulation is replaced in amber-colored vials and sealed with aluminum foil for the short term accelerated stability at 40˚±20˚C and 75±5% RH as per ICH state guidelines.
9. **Appearance:** *Insitu* nasal gel is examined visually for clarity in sol and gel form.
10. **pH of gel:** With the help of a pH meter pH of *in situ* nasal gel is measured.
11. **Measurement of Gelation Time:** 2 ml of formulation gel is taken in a test tube and kept in an oven at 37° C temperature. At exact time gelation of in situ gel is examined
12. **Critical Ionic Concentration (CIC):** Critical ionic concentration was an significant parameter of ionic in situ gel, indicating the least ionic concentration that promoted phase transition. Simulated nasal fluid (SNF) was prepared: 8.77 g NaCl, 2.98 g KCl, and 0.59 g CaCl2 were dissolved in 1 L distilled water. In 1 mL of

in situ gel solution, artificial nasal fluid was mixed in an ampoule, respectively. After 30 s, the gels are adhered to the bottom of bottles without flowing, shows that the gels formed. The normal physiological temperature of the human nasal cavity is 32°C–34°C. All measurements were taken at 34°C and made in triplicate.

13. **Water Holding Capacity:** 1 ml of the formulation was accurately transferred and put in a centrifuged EP tube that had been accurately weighed.250 µL of artificial nasal fluid was then added and mixed, respectively. The gel quality was accurately weighed and recorded as W0. This gel was centrifuged for 10 min at 8000 rpm, and the separate water layer was blotted by filter papers. The final gel quantity was weighed accurately and recorded as W. All measurements were taken at 34°C and tested in triplicate.

Water holding capacity = × 100%.

14. **TEM and SEM:** A small quantity of formulation was placed on the carbon film after dilution and dried for 12 h naturally. By using scanning electron microscopy the morphology of a formulation was studied. The formulation was lyophilized and then sprayed with gold for the observation.

15. **Gel strength determination:** Gel strength is spoken in terms of in seconds required by a 35g piston for penetration of 5cm distance, from the 50g gel formulation. This test was performed using the 'Gel strength apparatus' modified at the laboratory. Gel (50g) was placed in a 100 ml measuring cylinder. Gelation was induced by SNF. The apparatus for measuring gel strength (weight: 35g) was then placed onto the gel. The gel strength was slow as the time (in seconds) required moving the apparatus 5 cm down through the gel.

Table 5: Marketed products of Nasal in situ gels (8).

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

CONCLUSION

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

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