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ABSTRACT
The human nose has the potential to be an alternative route for the systemic delivery of a wide range of therapeutic agents. The richly supplied vascular nature of the nasal mucosa and its high drug permeation makes it a potential route for the administration of many drugs including proteins, peptides and vaccines. Nasal route is most suitable for those drugs which cannot be administered orally due to gastric degradation or hepatic first pass metabolism. In situ forming polymeric systems are formulations that are in sol form before administration into the body but once administered, undergo gelation in situ, to form a gel. The formation of in situ gel depends on factors like temperature, modulation, pH change, presence of ions etc. Temperature modulated gel is the widely accepted in situ formulation. The article provides a detailed review on the mechanism of in situ gel formation and the type of polymers used along with their evaluation. The uses of the strategies which enhance the nasal bioavailability are being used to formulate a number of drugs for delivery via the nasal route. A combination of mucoadhesive polymer along with thermoreversible polymer can be utilized for easy and safe delivery of therapeutic agents including biopharmaceuticals.

Keywords: Thermoreversible, Mucoadhesive, Nasal Drug Delivery (NDDS), Pluronic.

INTRODUCTION
The generation of a new drug molecule is an expensive and time consuming process. Hence the safety and efficacy ratio of “old” drugs can be improved by delivering these drugs at controlled and slow delivery or targeted delivery. This leads to the development of in situ gelling nasal drug delivery systems. In situ gel is drug delivery systems that are in sol form before administration in the body, but once administered, undergo gelation in situ, to form a gel.

Intra nasal administration has been accepted since ancient era, in the Ayurvedic system of Indian medicine. Many drugs have shown better systemic bioavailability through nasal route as they are significantly degraded in the GIT or undergo first pass effect in the liver. Due to the non invasive nature and increased patient comfort and compliance they are preferred for long term therapy as the parenteral route is considered inconvenient. Nasal drug delivery is suitable for restricting and obstacles blood brain barrier so that drugs can be delivered in the biophase of the CNS via the olfactory neurons which is viewed as a potential route for the administration of vaccines.

Table 1: Advantages of NDDS over oral and iv.

<table>
<thead>
<tr>
<th>Features</th>
<th>Nasal delivery</th>
<th>Oral delivery</th>
<th>I.V</th>
</tr>
</thead>
<tbody>
<tr>
<td>High serum drug levels</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid onset</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Titrable</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Painless</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Easy to use</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Nose
The nose performs three different processes like deposition, clearance or translocation & absorption of drugs which takes place inside the nose makes it a complex organ from kinetic point of view. The nasal septum divides the nasal cavity into two symmetrical halves. The nasal mucosa of the nose is the only location in the body that provides a direct connection between the central nervous system and the atmosphere. Drugs administered through the nasal mucosa rapidly traverse through the cribriform plate into the central nervous system by three routes.

- Directly by the olfactory neurons.
- Through supporting cells and surrounding capillary bed.
- Directly into the cerebrospinal fluid.

Figure 1: Anatomy of the nasal mucosa-cribriform plate interface.
Nasal cavity
The nasal cavity offers a number of unique advantages such as easy accessibility and good permeability especially for lipophilic, low molecular weight drugs. The nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 cm². These thermoreversible Drug delivery systems promotes the ease and convenience of administration, deliverance of accurate dose and also prolongs the residence time of drug in contact with mucosa, which are the problems that are encountered in semisolid dosage forms. 12

Respiration and olfaction is the major function of nasal cavity. The nasal cavity extends back from the outer nose into the head and connects with the sinuses which are the hollow areas. The nasal cavity is suffused with nasal hairs, which can filtrate and block larger particles from the inhaled air. The nasal cavity is covered with a thin and smooth layer of mucosa-nasal mucosa. The nasal mucosa is supplied with blood and glands that secrete fluids which can enhance the humidity and prevent the mucosa from being too dry. 13,14 The nasal cavity is divided by nasal septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. There are four areas in each symmetrical halves. 15-17

Nasal vestibule- region are very resistant to dehydration and limits permeation of substance due to the presence of stratified epithelial cells. 18

Atrium-it is a transitional epithelial region with stratified squamous cells anteriorly and pseudo stratified columnar cells and is less permeable to drug molecules due to small surface area and stratified cells.

Respiratory region-this region receives maximum secretions due to large number of pseudo-stratified columnar epithelia cells, seromucus glands, goblet cells and nasolacrimal duct. It is also richly supplied with blood vessels for heating and humidification of inspired air which make this region the most permeable in the nasal cavity.

Olfactory region-this area contains the peripheral organ of smell and act as a channel for the direct supply of drug to the brain. 19

Table 2: Advantages and limitations of drug delivery through nasal cavity 20-22

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ High degree of absorption and rapid transport of substance due to thin porous and highly vascularised epithelium</td>
<td>✗ Administration of only a small amount of the formulation is possible as large quantities creates problem for the normal functioning of the nose.</td>
</tr>
<tr>
<td>✓ Avoids the hepatic first pass metabolism.</td>
<td>✗ Surface area for absorption is smaller when compared to the GIT.</td>
</tr>
<tr>
<td>✓ Drugs can be targeted to the CNS bypassing the tight blood brain barrier.</td>
<td>✗ Drainage of the solution in the nasopharynx or expulsion of drug due to sneezing leads to irreproducibility of dosing regimen.</td>
</tr>
<tr>
<td>✓ Proteins and peptides can be safely delivered via this route due to the low enzymatic activity in the nasal cavity compared to the liver and GIT.</td>
<td>✗ Not appropriate for hydrophilic compounds and large molecules.</td>
</tr>
<tr>
<td>✓ Patient compliance and cost of therapy is low as nose is amenable to self medication.</td>
<td>✗ Possibility of irritation in the nasal mucosa.</td>
</tr>
<tr>
<td>✓ The risk of over dosage is low.</td>
<td>✗ Use of excipients like absorption enhancers in large amount may lead to toxicity problems.</td>
</tr>
<tr>
<td>✓ Bioavailability of small molecules is very good and that of larger molecules can be increased by the use of permeation enhancers.</td>
<td>✗ Drug administration is difficult in the case of pathological conditions like common cold and rhinitis.</td>
</tr>
</tbody>
</table>

Nasal mucosa
It lines the entire nasal cavities and is continuous with the adjoining cavities to which the nasal cavity communicates (e.g. the nasopharynx and paranasal sinuses) except for the vestibule of nose and is firmly bound to the peristomeum and perichondrium of the supporting structures of the nose. The anterior nasal cavity is lined with stratified squamous and transitional epithelium, and the highly vascular respiratory epithelium is mostly ciliated, columnar and stratified (Mygrind et al., 1982).
Mechanism of nasal absorption

The first step in the absorption of drugs from the nasal cavity is the passage through the mucus. Small unchanged particles easily pass through this layer while large charged particles find it more difficult to cross. The primary protein present in mucus is mucin which has a tendency to bind to solutes which in turn hinder diffusion. Also structural changes due to environmental changes like pH, temperature, etc are also possible. The passage of drug through the mucus has been explained by several mechanisms such as transcellular or simple diffusion across the membrane, paracellular transport which occurs between cells and transcytosis which involves vesicle carriers cellular transport out of which two are considered important. Potential metabolisms before reaching the systemic circulation and limited residence time in the nasal cavity are the major obstacles for drug absorption.

23–25

a) First mechanism- also known as paracellular transport this utilizes the aqueous route of transport and is slow and passive. This route is not suitable for the drugs having molecular weight greater than 1000 Daltons due to poor bioavailability.26

b) Second mechanism- also known as transcellular route which utilizes the lipoidal route for transport of lipophilic drugs.

c) Drugs also cross cell membranes by an active transport route via carrier mediated or transport through the opening of tight junctions.

E.g. chitosan a natural biopolymer from shell fish opens tight junctions between epithelial cells to facilitate transport.27

Figure 3: Intercellular spaces, (A2) Tight junctions, (B1) Passive diffusion, (B2) Active transport, (C) Transcytosis.

In situ forming polymeric delivery systems

These are the novel drug delivery systems that favour the ease and convenience of administration and delivery of accurate dosage forms which are the major problems encountered by the normal semi solid dosage forms. Ordinary gels are difficult to administer and an accurate dose cannot be measured while mucoadhesive powders are not highly favored products as they can cause irritation on the nasal mucosa and give a gritty feeling to the tissues. An in situ mucoadhesive gel appears to be very attractive since they are fluid like prior to administration which makes them easy to administer as a drop allowing accurate dosing.28–29

Figure 4: Advantages of in situ polymeric system

Formulation of in situ gels depends on various physical and chemical stimuli like temperature modulation, pH change, solvent exchange, electric field, light, magnetic field, presence of ions and ultraviolet radiation from which the drug gets released in a sustained and controlled manner. Among them temperature responsive systems are the most important as they are predominantly studied. Smart polymeric systems provide promising means of delivering these drugs. Various natural and synthetic polymers are used for the preparation of in situ gels which undergoes a sol-gel transition when administered.

Principle involved in in-situ gelling

The principle involving the in situ gelling of solid nasal formulations is that the nasal formulations imbibe the nasal fluid after administration and forms gel in the nasal cavity. The avoidance of foreign body sensation is an advantage in the case of nasal gels. The bioadhesive properties of the gels helps in keeping the gel and mucosa intact which also acts as a release controlling matrix system. This helps in the sustained delivery of drugs. In the nose the mucus 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 0.5mm. ciliary activity zones then occur at various intervals. Cilia situated backward helps to remove any obstacle if there is any interference in the propulsion phase. After the formation of gel, dissolution occurs and or the mucociliary removal towards the nasopharynx occurs. Therefore there is no need to remove the dosage form after it has been depleted of drug.30, 31

Figure 5: principle of solid in situ gelling nasal formulation.
Polymers used in thermoreversible in situ formulations

1. Pluronics or Poloxamers

These are a class of thermoreversible gels that have the capacity to make, break and modify the bonds responsible for holding the network together. There are different classes of Pluronics (pluronic F-127, F-188 etc.). Their thermoreversible property make them useful as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. The potential use of PF-127 as an artificial skin has also been reported. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20-30%. These polymers are produced by condensation of ethylene oxide and propylene oxide. These are white, waxy, free flowing granules that are practically odorless and tasteless. Reverse thermal gelation and low toxicity have been the basis of research into the use of PF-127 as a possible drug delivery system in man.

2. Carbopol

They are very high molecular weight polymers of acrylic acid and are used mainly in liquid or semisolid pharmaceutical formulations such as gels, suspensions and emulsions, as a thickening and viscosity agent in order to modify the flow characteristics. They are also used for mucoadhesive properties and a relevant amount of work has been done on the bioadhesive potential of carbopol polymers. Carbopol are used in formulations for ophthalmic, rectal, buccal, nasal, intestinal, vaginal and topical preparations. Carbopol gels are prepared by the dispersion of polymers in water. In which it swells upto1000 times the original volume (BF Goodrich handbook) and neutralizes the system. It permits the ionization of the carboxylic groups and as a result strong gel forms.

3. Chitosan

Chitosan is a biodegradable, thermo-sensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyl salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.

4. Gellan gum

Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrascaride repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The formulation consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in
situ. In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported. 54

5. Xanthan gum
Xanthan gum is a high molecular weight extra cellular 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-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain. 55

6. Alginic acid
It is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages. The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Lglucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegradability and nontoxicity. A prolonged preconeral residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesive properties. 56,57

Table 3: Some nasal mucoadhesive delivery systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mucoadhesive polymer</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metochlopramide hydrochloride</td>
<td>Poloxamer407/Polyethylene glycol</td>
<td>Gel</td>
</tr>
<tr>
<td>Metochlopramide hydrochloride</td>
<td>Carbopol 981</td>
<td>Solution, Gel, Powder</td>
</tr>
</tbody>
</table>

Evaluation of in situ gels

In vitro nasal permeation studies
The in-vitro permeation studies are performed by the diffusion studies in a diffusion cell made of glass which consists of a donor and receiver compartment. The nasal mucosa of the sheep is used in the diffusion studies. 58

In Vivo Nasal Absorption studies
A number of animal models are used for the in-vivo studies: these include the rat model, rabbit model, dog model, sheep model, monkey model.

Gelation temperature
It is defined as the temperature at which the liquid phase makes a transition to gel, and is determined by placing a specific quantity of the formulation into a transparent vial containing a magnetic bar. The vial was heated at a constant rate. The gelation temperature was measured when the magnetic bar stops. 59

Gel strength
It is evaluated using a rheometer. Depending on the mechanism of gelling of the gelling agent used a specific amount of the gel is placed in a beaker and is raised at a certain rate so pushing a probe slowly through the gel. The changes in the load of the probe can be measured as a function of depth of immersion of the probe below the gel surface. 60

Drugs those are suitable to be administered by nasal route
The intra nasal administration is a promising route for the administration of systemically acting drugs with poor bioavailability. Antimigraine drugs, peptide drugs (hormone treatments), anesthetics, anti emetics, vasopressin, corticosteroids, sedatives, narcotics and a number of drugs can be administered by this route.

CONCLUSION
Developments in the field of polymer science have lead to the emergence of various stimuli sensitive hydrogels like pH, temperature formulations which are used for targeted drug delivery.

Sustained and prolonged release of the drug, stability and biocompatibility makes the in situ systems very reliable. Due to the extensive research in the nasal delivery, nasal formulations have acquired the fourth position in the market. Soon it is expected that this will grow further within next few years. In the in situ gelling nasal formulations, there is no need to remove the dosage form from the nasal cavity; therefore these formulations will become the efficient way of drug delivery. In the future, the in situ gelling nasal drug delivery will continue to advance and will represent a viable alternative to the oral and injectable routes of administration. Drugs for acute and long term diseases and novel nasal vaccines with better local or systemic protection against infections will be available. The development of drugs that directly target the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects is also in the pipeline.

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