A REVIEW ON NASAL DRUG DELIVERY SYSTEM

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ABSTRACT
There are several routes of drug administration such as oral, transdermal, parenteral, rectal, ocular, intra-vaginal, nasal etc. Amongst them nasal drug delivery shows great impact. Recently, it has been shown that many drugs have better bioavailability by nasal route than by oral route because it has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa. Intranasal route of administration shows potential for delivery of drugs to brain. The nose-to-brain drug delivery of drugs is advantageous as it requires low dose of drug, avoids first pass effect. Also it is fast in action and suitable for the drugs that degrade in gastrointestinal tract. However, the major limitation with nasal route administration is the poor contact of the formulations with the nasal mucosa due to mucoceliary clearance. Many attempts have been done in the recent past to increase the residence time of drug formulations in the nasal cavity, resulting in improved nasal drug absorption by using mucoadhesive polymers.

Key words: - Nasal drug delivery, Insitu gel, polymers used in gel preparation, mucoadhesive polymer.

INTRODUCTION
Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration or any other route of administration1,2 Nasal mucosa has been considered as a potential...
administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. The greater permeability of nasal mucosa with large surface area affords a rapid onset of therapeutic effect. The low metabolic surroundings of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. In addition to that, nasal administration minimizes the lag time associated with oral drug delivery and offers non-invasiveness, patient comfort, self-administration and patient compliance, which are the barrier in intravenous drug therapy. The appealing advantage of nasal drug delivery is the possibility of targeting central nervous system (CNS) by bypassing blood brain barrier [3] (BBB). The drugs absorbed nasally via olfactory epithelium are reported to enter in olfactory neurons and supporting cells and subsequently into the brain, which reduced not only the systemic toxicity of centrally acting drugs but also enhanced therapeutic efficacy. [4] The nasal route has received great interest as a route for vaccination. [5] Nasal delivery of suitable antigen along with proper adjuvant to the nasal associated lymphoid tissue (NALT) has potential to induce humoral and cell mediated immunity. Nasal route is the route of choice for rapid mass immunization in developing countries [6]. Intranasal immunization may lead to the development of local, as well as systemic immunity. [7] Despite having large number of advantages, bioavailability of nasal dosage form is hindered by various physicochemical, physiological and formulation factors. [8]

NASAL ANATOMY AND PHYSIOLOGY (7)

In studying drug absorption from the nasal mucous membrane, it is necessary to have a clear understanding of anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used [7,8,9]. The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12-14 cm. In this passage the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. There are 3 separate functional zones in the nasal cavities, vestibular, respiratory and olfactory regions [8,9].

The zones are arranged anteroposteriorly in the sequence of order. The vestibular area serves as a baffle system and its surface is covered by a common pseudo stratified epithelium where
the long hairs may provide the function of filtering air borne particles. Respiratory area has a surface lined by a pseudo stratified columnar epithelium and is normally covered by a dense layer of mucus that is constantly moving towards the posterior apertures of the nasal cavity by a powerful system of motile cilia\textsuperscript{[8,9]}. The olfactory segment is lined with a specialized type of pseudo stratified columnar epithelium known as olfactory epithelium, which contains receptors for the sense of the smell. This segment is situated along the dorsal roof of the nasal cavity. Olfactory mucosal cell types include: bipolar neurons, supporting (sustentacular) cells, basal cells and Bowman's glands. The axons of the bipolar neurons form the olfactory nerve (cranial nerve I). Bowman's glands are serous glands in the lamina propria, whose secretions entrap and dissolve odoriferous substances\textsuperscript{[10,11,12]}. The total surface area of both nasal cavities is about 150 cm\textsuperscript{2} and the total volume is about 15 ml.

Each of the two nasal cavities is limited by the septal wall and the lateral wall dominated by superior, middle and inferior turbinate (Fig. 1). They are important for maintaining the slit like cavity thus facilitating humidification and temperature regulation of inspired air. Under and on the side to each of the turbinates are passages called the inferior, middle and superior meatus. The inferior and middle meatus receive the openings of the nasolacrimal duct and the paranasal sinuses.\textsuperscript{[13,14]}

**Nasal Epithelium**

The nostrils are covered by skin, the anterior one-third of the nasal cavity by a squamous and transitional epithelium, the upper part of the cavity by an olfactory epithelium and the remaining portion by a typical airway epithelium which is ciliated, pseudostratified and columnar\textsuperscript{[11,12]}.

The epithelial cells in the nasal vestibule are stratified, keratinized and squamous with sebaceous glands. Due to its nature, the nasal vestibule is very resistant to dehydration and can withstand noxious environmental substances red by cilia. Another cell type, and limits permeation of substances. The atrium is a middle epithelial region with stratified, squamous cells anteriorly and pseudostratified columnar cells with microvilli posteriorly.\textsuperscript{[13]}
The nasal airway epithelium consists of four major cell types: basal cells, ciliated and nonciliated columnar cells, goblet cells and basement membrane. Basal cells are the progenitors of the other cell types and lie on the basement membrane and do not reach the airway lumen. They are supposed to help in the adhesion of columnar cells to the basement membrane. Columnar cells are related to neighbouring cells by tight junctions apically and in the uppermost part by interdigitations of the cell membrane. All columnar cells, ciliated and non-ciliated are covered by about 300 microvilli uniformly distributed over the entire apical surface. These short and slender fingers like cytoplasmic expansions increase the surface area of the epithelial cells thus promoting exchange processes across the epithelium. The microvilli also avoid drying of the surface by retaining moisture essential for ciliary function. The cilia have a typical ultra structure, each ciliated cell containing about 100 cilia, 0.3 µm wide and 5 µm in length. The anterior one-third of the nasal cavity is non-ciliated.\cite{14}

Cilia start occurring just behind the front edge of the inferior turbinate and the posterior part of the nasal cavity as well as the paranasal sinuses is densely cove characteristic of an airway epithelium is the goblet cell. The goblet cell contribution to the volume of nasal secretion is probably small compared to that of the submucosal glands. Goblet cells most likely respond to physical and chemical irritants in the microenvironments. The basement membrane is the layer of the collagen fibrils on which the epithelium rests. The olfactory epithelium is a pseudostratified columnar in type and consists of specialized olfactory cells, supporting cells and both mucous and serous gland. The olfactory cells are bipolar neurons and act as peripheral receptors and first-order ganglion cells.\cite{13,14,15}
Blood Supply to Nasal Cavity\textsuperscript{[13]}

Nasal vasculature is richly supplied with blood to fulfill the basic functions of the nasal cavity such as heating and humidification, olfaction, mucocilliary clearance and immunological functions. Blood supply comes from branches of both the internal and external carotid artery including branches of the facial artery and maxillary artery. The named arteries of the nose are,

- **Sphenopalatine artery**, a branch of maxillary artery.
- **Anterior ethmoidal artery**, a branch of ophthalmic artery.
- **Branches of the facial artery** supplying the vestibule of the nasal cavity.

The lamina propria in the nasal mucosa is rich in blood vessels. They differ from the vasculature in the tracheobronchial tree in three ways. First is venous sinusoid in the nose. Second is arteriovenous anastomosis in the nose. Third are the nasal vasculature shows cyclical changes of congestion giving rise to the nasal cycle. Porosity of the endothelial basement membrane has been described as a characteristic of nasal blood vessels. The capillaries just under the surface epithelium and surrounding the glands are well suited for rapid movement of fluid through the vascular wall.

Mucus Secretion and Mucociliary Clearance\textsuperscript{[14]}

The submucosal glands which secrete the greater quantity of nasal mucus comprise both mucus cells, secreting the mucus gels and serous cells, producing a watery fluid. Mucus is also released from the goblet cells as mucus granules which swell in the nasal fluids to contribute to the mucus layer. Mucus secretion is a compound mixture of many substances and consists of about 95% water, 2% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulin, lysozyme and lactoferrin and <1% lipids. About 1.5 to 2 litre of nasal mucus is produced daily. This mucus blanket about 5 mm thick consists of two layers, an upper gel layer and lower sol layer. The viscosity of both layers affects ciliary beating and the efficiency of transporting the overlying mucus, the mucociliary clearance (MCC). The nasal mucus performs a number of physiological functions,

- It acts as adhesive and transports particulate matter towards the nasopharynx.
- It behaves as an adhesive.
- It acts as a retainer for the substances in the nasal duct.
- It covers the mucosa and physically and enzymatically protects it.
- The mucus has water-holding capacity.
- It exhibits surface electrical activity.
It permits efficient heat transfer.

### Table 1: Structural feature of different section of nasal cavity and their impact on permeability\[^{24}\]

<table>
<thead>
<tr>
<th>Region</th>
<th>Structural Features</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal vestibule</td>
<td>Nasal hairs (vibrissae) Epithelial cells are stratified, squamous and keratinized sebaceous glands present</td>
<td>Last permeable because of the presence of Keratinized cells</td>
</tr>
<tr>
<td>Atrium</td>
<td>Transepithelial region stratified squamous cells present anteriorly and pseudo stratified cells with microvilli present posteriorly</td>
<td>Less permeable as it has small surface area and stratified cells are present</td>
</tr>
<tr>
<td>Respiratory region</td>
<td>Pseudostratified ciliated columnar cells with microvilli (300per cell), large surface area Receives maximum nasal secretion because of the presence of seromucus gland, nasolacrimal duct and goblet cells</td>
<td>Most permeable region because of large surface area and rich vasculature</td>
</tr>
<tr>
<td>Olfactory region</td>
<td>Specialized ciliated olfactory nerve cells for smell perception Receives ophthalmic and maxillary division of trigeminal nerve Direct access to cerebrospinal fluid</td>
<td>Direct access to cerebrospinal fluid</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Upper part contains ciliated cells and lower part contains squamous epithelium</td>
<td>Receives nasal cavity drainage</td>
</tr>
</tbody>
</table>

**INTRANASAL DRUG DELIVERY \[^{15, 16, 17}\]**

Over the last years, due to the understanding of the positive attributes and appropriate characteristics of the nasal cavity, intranasal route has been increasingly considered for drug delivery when developing new chemical entities or improving the therapeutic profile of existing drugs. However, to assess the therapeutic viability of intranasal drug delivery several approaches should be considered, specifically, to the nature of pathologic condition (acute or chronic) and intended effects of drug treatment (local, systemic or at CNS). Indeed, for acute disease conditions, the advantages afforded by intranasal drug delivery in terms of patient comfort and compliance may not be much relevant when compared with drug delivery by parenteral route. In contrast, this is particularly important to treat or control chronic medical conditions \[^{16}\]

**Intra-nasal drug delivery systems \[^{17, 18, 19}\]**

1) Local delivery
2) Systemic delivery
3) Nasal vaccine
4) CNS Delivery through Nasal Route

**Various Dosage Forms given by Nasal Route**, [20]

1. Solution and sprays
The drug solution are administered nasally as nasal drops, sprays and as a meter dose nebulizer. The dose of active ingredient depends on the volume of drug and the concentration of drug in the formulation. [21, 22, 23]

2. Suspension [24]
Suspensions for nasal administration are prepared by suspending the micronized drug in a micronized drug in a carrier suitable for application to the nasal mucosa.

3. Powder [25, 26, 27, 28]
Powder dosage form of drug for nasal administration offers several advantages over liquid formulation. The chemical stability of the drug is increased, preservative in the formulation is not required and it is possible to administered large doses of drug

4. Nasal particulate drug delivery system [29, 30, 31, 32]

- **Microparticle and Nanoparticle**
Nasal particulate systems using polymers as carriers include microparticle/sphere and nanoparticle. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, enhance the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium, and act as a controlled release system resulting in prolonged blood concentrations. polymers which are used as nasal drug particulate carrier, +ve charged polymer such as Chitosan and gelatin.

5. Semi-solid dosage form [33, 34]
Gel preparation is soft, solid or solid like material consists of two or more component one of which is liquid. The gelation occurs through the cross-linking of polymer chains, it can be achieved by covalent bond formation (chemical cross-linking) or non-covalent bond formation (physical cross-linking). Gel formulations with suitable rheological properties increase the contact time with the mucosa at the site of absorption. The improved contact time is caused by the mucoadhesive properties of the polymer in the gel.
GEL PREPARATION
Drug delivery to the nasal mucosa faces several difficulties. One of these is from the effective clearance mechanisms present in the nose. Polymer with suitable rheological properties can facilitate the absorption of poorly absorbed drugs by increasing the mucoadhesive properties of the gel. Low permeability through the nasal membrane, various pathological conditions like cold and allergic reaction which may alter the absorption. To overcome this limitation component which is use in formulation should be minimum toxic to nasal mucosa. Additionally there should be use permeability enhancer to enhance permeability of macro molecule thought the nasal mucosa. And also provide the maximum biodhesive /mucoadhesive strength to minimize the clearance effect. To achieve all this novel approach of in-situ gel system where found to be effective and advantageous

Advantages \[35,36\]
1) Drugs that are orally not absorbed can be delivered to the systemic circulation by means of nasal drug delivery.
2) Avoid hepatic first pass metabolism.
3) Easy accessibility and needle free drug application without the necessity of trained personnel facilitates self medication, thus improving patient compliance compared to parenteral routes.
4) Drug degradation that is observed in the gastrointestinal tract is absent.
5) The bioavailability of large drug molecules can be improved by means of absorption enhancer or other approach.
6) Rapid drug absorption and quick onset of action can be achieved.
7) The nasal bioavailability for smaller drug molecules is good.
8) Drug possessing poor stability in GIT fluids are given by nasal route.
9) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
10) Polar compound exhibiting poor oral absorption may be particularly suited for this route of delivery.
11) Suitable for the patients, especially for those on long term therapy, when compared with parenteral medication.

Disadvantages \[36-38\]
1) Nasal cavity provides smaller absorption surface area when compared to GIT
2) Inconvenient to patient when compared to oral delivery system since there is a possibility of irritation.
3) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
4) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of improper technique of administration.
5) Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.

**IN-SITU GEL**

In-situ gel formulations are drug delivery systems that are in solution form before administration in the body, but after administration it undergo gelation to form a gel. This can be achieved by using different polymers such as Chitosan, PVA, Poloxamer 407, Xanthan gum, Gellan gum, HPMC with different grade, Carbopol. The formation of gels depends on factors like pH change, temperature modulation, ultra violet irradiation and presence of ions, from which the drug gets released in a sustained and controlled manner. In-situ forming drug delivery system possesses some advantages like ease of administration, simple manufacturing process and improved bioavailability. Therefore, this system combines the advantages of both solution and gel such as ease of administration and prolonged the residence time so that it provides improved patient compliance, dosing frequency reduce and bioavailability. As there are various polymers used for preparation of such system they must be possess ideal characteristics.

**Table no:2 Polymers used for the preparation in-situ gelling system:**

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Origin</th>
<th>Charge</th>
<th>Solubility</th>
<th>Mucoadhesive capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pH sensitive polymers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbomer</td>
<td>Synthetic</td>
<td>Anionic</td>
<td>Insoluble</td>
<td>+++</td>
</tr>
<tr>
<td>Polyacrylic acid</td>
<td>Natural</td>
<td>Anionic</td>
<td>Insoluble</td>
<td>+++</td>
</tr>
<tr>
<td>Cellulose acetate phthalate</td>
<td>Synthetic</td>
<td>Nonionic</td>
<td>Insoluble</td>
<td>++</td>
</tr>
<tr>
<td><strong>Temperature sensitive polymer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poloxamer</td>
<td>Synthetic</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>++</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>Natural</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Natural</td>
<td>Cationic</td>
<td>Soluble</td>
<td>++</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>Natural</td>
<td>Nonionic</td>
<td>Soluble</td>
<td>+</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>----------</td>
<td>---------</td>
<td>---</td>
</tr>
<tr>
<td>Ion sensitive polymer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Natural</td>
<td>Anionic</td>
<td>Insoluble</td>
<td>+</td>
</tr>
<tr>
<td>Gellan gum (Gelrite)</td>
<td>Natural</td>
<td>Anionic</td>
<td>Soluble</td>
<td>++</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Natural</td>
<td>Cationic</td>
<td>Insoluble</td>
<td>++</td>
</tr>
</tbody>
</table>

**Ideal Characteristics of Polymers**

- It should be non-toxic.
- It should be biodegradable.
- It should be biocompatible.
- It should have mucoadhesive properties.
- It should have good tolerance

**CLASSIFICATION OF IN-SITU GELLING SYSTEM** [35,38,39]

1) pH sensitive in situ gelling system
2) Temperature sensitive in situ gelling system
3) Ion sensitive in situ gelling system
4) Electrical signal sensitive in situ gelling system

- **pH sensitive in situ gelling system:**
  In this system there is a major role of pH in gelling of solution. Gelling is triggered by change in or shift in pH, when the pH is raised from 5-7.4. At higher pH polymers forms hydrogen bond with mucin, which leads to hydrogel formation.

  **Mechanism:** All the polymer which are pH sensitive contain acidic or basic groups that can either accept or release proton in response to change in environmental pH. In case of weakly basic groups swelling of hydrogel is decreases as the external pH is increases while increases in case of weakly acidic group.

- **Temperature sensitive in situ gelling-**
  This system is liquid solution at room temperature i.e. 25-27°C and when it comes in contact with body fluid (35-37°C) undergoes gelation due to change in temperature. Temperature sensitive gels are three types:
1. Positive temperature sensitive gel: - It has an upper critical solution temperature such gel contracts on cooling below UCST.
2. Negative temperature sensitive gel: - It has lower critical solution temperature such gel contracts on heating above LCST.

3. Thermally reversible gel

Mechanism:- Upon increasing the temperature phase transition occurs sol to gel due to three mechanisms, increased micellar aggregation, desolvation the polymer, and increased entanglement chain degraded. Leads to the formation of hydrogel and phase transition occurred.

- **Ion sensitive in situ gelling:** The gelation is triggered by the presence i.e. Na+, Mg++, Ca++ in the fluid. This can be achieved by various polymers. The gelation is occurred by ionic interaction of polymer and divalent ions of fluid. When the anionic and cationic polymer comes in contact it converts to form a gel.

- **VARIOUS POLYMERS USED IN PREPARATION OF IN SITU GELLING SYSTEM**

Polymers Used In pH Sensitive In Situ Gelling System

- **Carbomer**[^39]

![Scheme 1: Structure of Carbomer](image)

It is high molecular weight, cross linked polyacrylic acid derivative and has a strong mucoadhesive property. Carbopol polymers are having very good water sorption property. They swell in water up to 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0 to 6.0 because the pKa
of these polymers is 6.0 ± 0.5. As the Carbomer concentration increased, it becomes acidic in nature and may cause irritation. If there is an addition of cellulose then it will reduce polymer concentration and improve gelling property. Carbopol are manufactured by cross-linking process. Depends on the degree of cross-linking and manufacturing conditions, various Carbopol grades are available. Each grade is having its significance for its usefulness in pharmaceutical dosage forms which include Carbopol 934 and Carbopol 981 mostly used for gelling purpose

**Mechanism:** The mucoadhesive property is due to electrostatic interaction or hydrophobic interaction, hydrogen bonding. It is acidic molecule. When dispersed in water, carboxylic group of the molecule partially dissociate and form a coil. As it is pH sensitive polymer, increase in pH of solution result in swelling of polymer. The gelling effect is activated in two stages, neutralization of solution by addition of, sodium hydroxide or potassium hydroxide, triethanolamine.

- **Polycarbophil**[^40]
  It is lightly cross linked polyacrylic acid having excellent mucoadhesive property. The gelling of polymer also depends on pH of solution.

**Mechanism:** It is insoluble in water but its swelling capacity in neutral medium permits the entanglement of polymer chain with mucus layer. The carboxylic acid group of polycarbophil binds to mucin by hydrogen bonds. Cellulose acetate latex (CAP latex) another pH sensitive polymers these are flowing liquid at pH 4.8 and gel at pH 7.4.

**Polymers Used In Temperature Sensitive Gelling System:**

*Cellulose Derivative*

![Scheme 2: Structure of HPMC](image-url)
**Properties:** Cellulose is composed of repeating β-(1,4)-D-glucopyranose unit in glucan chain. Natural polymers like HPMC, MC, HPC and EC exhibit temperature sensitive sol-gel phase transition.[44] When temperature is decreases cellulose material will increases its viscosity while its derivatives like HPMC, MC will increase its viscosity when temperature is increased[45]. MC is composed of native cellulose with alternate methyl substitution group on its chain. At low temperature (30°C) solution is in liquid form and when temperature is increases (40-50°C) gelation occurred.

**Mechanism:**- Cellulose solution is converts into gelation by hydrophobic interaction between molecules containing methoxy substitution. At high temperature, polymers lose their water of hydration whereas.[44] at low temperature, molecules are hydrated and little polymer-polymer interaction occurs.

*Poloxamer* [41]

![Scheme 3: Structure of Poloxamer](image)

Poloxamer are water soluble tri-block copolymer consisting of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration.

**Properties:** Poloxamer commercially also known as Pluronic® and has good thermal setting property and increased drug residence time. It is used as gelling agent, and solubilizing agent. Poloxamer gives colorless, transparent gel. Depending upon the ratio and distribution of hydrophilic and hydrophobic chain several molecular weights available, having different gelling property.[41]
Table 3: Poloxamer grades

<table>
<thead>
<tr>
<th>Poloxamer</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>124</td>
<td>2200</td>
</tr>
<tr>
<td>188</td>
<td>8400</td>
</tr>
<tr>
<td>237</td>
<td>7959</td>
</tr>
<tr>
<td>338</td>
<td>14600</td>
</tr>
<tr>
<td>407</td>
<td>12600</td>
</tr>
</tbody>
</table>

**Mechanism:** It consists of central Polypropylene oxide (Hydrophobic part) surrounded by Polyethylene oxide (Hydrophilic part). At room temperature (25°C), it behaves as viscous liquid and is transformed to transparent gel when temperature increases (37°C). At low temperature, it forms small micellar subunit in solution and increases in temperature results increase in viscosity leads to swelling to form large micellar cross linked network.

- **Xyloglucan**
  Xyloglucan is composed of (1,4)-β-D- glucan back bone chain(GLC) with (1,6)-α-D- xylose branches (XYL), partially substituted by (1-2)-β-D- galactoxylose (GAL). It is water soluble hemicelluloses obtained from vascular plants and it exhibit thermally responsive behavior when more than 35% galactose residues are removed.[39,40]

**Properties:** Xyloglucan is consists of three different oligomers like heptasaccharide, octasaccharide, nonsaccharide, which differ in number of galactose side chain. It is non-toxicity, biodegradable and biocompatible property. Like poloxamer it exhibit gelation on heating refrigerator temperature or cooling from a higher temperature. But the difference is xyloglucan forms gel at lower concentration (1-2% wt).

**Mechanism of gelling action:** The native form of xyloglucan does not show gelation, its dilute solutions form sol-gel transition on heating due to partial degradation of β-galactosidase. The transition temperature is inversely related to galactose removal ratio and polymer concentration.[42]
Chitosan is a natural polymer obtained by deacetylation of chitin, it is a cationic polysaccharide consisting copolymers of glucosamine and N-acetyl glucosamine. Chitosan has mucoadhesive property due to electrostatic interactions between positively charged amino group and negatively charged mucin. It is non toxic, biocompatible, biodegradable polysaccharide and having bioadhesive.

**Mechanism:** Chitosan has mucoadhesive property is due to the formation of ionic interaction between the positively charged amino groups of chitosan and negatively charged sialic acid residues of mucins, depends on environmental pH. Because of its bioadhesive, hydrophilic, good spreading properties.

**POLYMERS USED FOR ION SENSITIVE IN SITU GELLING SYSTEM:**
- Deacetylated gellan gum (Gelrite)

Scheme 4: structure of Chitosan

Scheme 5: structure of Gelrite
Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and are linked together to give a tetrasaccharide unit.

**Properties:** Gelrite is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Upon instillation, gelrite forms gel due to the presence of calcium ions. The gelation involves the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks by complexation with cations and hydrogen bonding with water. Because of its thixotropy, thermo plasticity, pseudo plasticity are widely use in food industry.

**Mechanism:** Gellan gum produce a cation induced in situ gelation (Ca\(^{2+}\), Mg\(^{2+}\), K, Na\(^{+}\)) due to the cross linking between negatively charged helices and mono or divalent cations (Na\(^{+}\), Ca\(^{+}\), Mg\(^{+}\)). Divalent ions superior to promoting gelation as compared to monovalent cations. Gelation prolongs the residence time of drug at absorption site and bioavailability of the drug is increased.\[^{[41]}\]

- **Sodium Alginate**\[^{[45]}\]

![Scheme 6: structure of sodium alginate](image)

**Properties:** Sodium alginate is a salt of alginic acid and extracted from brown algae. It is a linear block polysaccharide consisting of two type monomers β-D-Mannuronic acid and α-L-glucuronic acid residues joined by 1,4 glycosidic linkages. It is biodegradable and non toxic and exhibit good mucoadhesive property due to its carboxylic group.
Mechanism: The monomers of alginate (β-D-mannuronic acid (M) and α-L-glucuronic acid (G) are arranged as M-M block or G-G block with alternating sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties resulting in the formation of homogenous gel. Mechanical strength and porosity of hydrogel depends on G:M ratio, type of cross linker used and concentration of alginate solution.

MUCAODHESIVE DRUG DELIVERY SYSTEM

Mucoadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces. During the 1980s, this concept began to be applied to drug delivery systems. It consists of the incorporation of adhesive molecules into some kind of pharmaceutical formulation intended to stay in close contact with the absorption tissue, releasing the drug near to the action site, thereby increasing its bioavailability and promoting local or systemic effects.

Mechanisms of Mucoadhesion

The mechanism of adhesion of certain macro-molecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. Hydration of the polymer plays a very important role in Bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration there is a dissociation of hydrogen bonds of the polymer chains. The polymer-water interaction becomes greater than the polymer-polymer interaction thereby making the polymer chains available for mucus penetration. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure.

Theories Of Mucoadhesion

Electronic Theory: The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical charge forms at the interface and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.
Adsorption Theory: The adsorption theory of bioadhesion proposes that adhesion of a polymer to a biological tissue results from (i) primary chemical bonds that are somewhat permanent and therefore undesirable in bioadhesion (ii) van der Waals, hydrogen, hydrophobic and electrostatic forces which form secondary chemical bonds.

Wetting Theory: Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer or use of a surfactant.

Diffusion Theory: The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers and the diffusion co-efficient is known to depend on molecular weight and cross-linking density.

Factors Affecting Mucoadhesion
The mucoadhesive power of a polymer is affected by the nature of the polymer and also by the nature of the surrounding media. The factors influencing the mucoadhesion are as follows,

I. Polymer Related Factors
- Molecular weight
- Concentration of active polymer
- Flexibility of polymer chains
- Special confirmation
- Swelling

II. Environment Related Factors
- pH of the polymer-substrate interface
- Applied strength
- Initial contact time

III. Physiological Factors
- Mucin turnover
- Disease state
Advantages of Mucoadhesive Drug Delivery Systems (49,50,51)

1. These dosage forms are readily localized in the region applied to improve and enhance the bioavailability of drugs.

2. The dosage forms facilitate intimate contact of the formulation with the underlying absorption surface. This allows modification of the tissue permeability for absorption of macromolecules such as peptides and proteins. Inclusion of penetration enhancers such as sodium glycolate, sodium taurocholate and protease inhibitors in the mucoadhesive dosage forms resulted in the better absorption of the peptides and proteins.

3. Mucoadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.

Mucoadhesive Polymers (52,53)

Bioadhesive polymers have been used extensively in nasal drug delivery systems to provide dosage forms retention. Bioadhesive polymers are defined as polymers that can adhere to a biological substrate. Diverse classes of polymers have been investigated for their potential use as mucoadhesive.

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks joint by cross linking agents. The polymers should possess optimal polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. (table no.4)

Ideal polymers for mucoadhesive drug delivery system should have the following characteristics,

- The polymers and its degradation products should be nontoxic and non-absorbable from the gastrointestinal tract.
- It should possess an optimum molecular weight to the Bioadhesion.
- It should be able to accommodate both oil and water soluble drugs for the purpose of controlled drug delivery.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.
- It should show specificity for attachment to an area or cellular site.
- It should show specificity and stimulate endocytosis.
- It should be inert and compatible with the environment.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.
• It should possess a wide margin of safety both locally and systemically.
• It should be a nonirritant to the mucous membranes.
• It should preferably form a strong noncovalent bond with the mucin epithelial cell surface.
• It should adhere quickly to moist tissue and should possess some site specificity.
• It should allow easy incorporation of the drug and offer no hindrance to its release.
• The polymer must not decompose on storage or during shelf life of the dosage form.
• The cost of the polymer should be not too high, so that prepared dosage form remains competitive.

Table no.4 Mucoadhesive Polymers Used In Nasal Drug Delivery[^54]

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Bioadhesive property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxymethylcellulose</td>
<td>+ + +</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>+ + +</td>
</tr>
<tr>
<td>Polycarbophil</td>
<td>+ + +</td>
</tr>
<tr>
<td>Tragacanth</td>
<td>+ + +</td>
</tr>
<tr>
<td>Poly(acrylic acid/divinyl benzene)</td>
<td>+ + +</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>+ + +</td>
</tr>
<tr>
<td>Hydroxy ethyl cellulose</td>
<td>+ + +</td>
</tr>
<tr>
<td>Gum karaya</td>
<td>+ +</td>
</tr>
<tr>
<td>Thermally modified starch</td>
<td>+ +</td>
</tr>
<tr>
<td>Pectin</td>
<td>+ +</td>
</tr>
<tr>
<td>Polyvinyl pyrroldene</td>
<td>+</td>
</tr>
<tr>
<td>Acacia</td>
<td>+</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>+</td>
</tr>
<tr>
<td>Psyllium</td>
<td>+</td>
</tr>
<tr>
<td>Amberlite-200 resin</td>
<td>+</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>+</td>
</tr>
<tr>
<td>Chitosan</td>
<td>+</td>
</tr>
</tbody>
</table>

**REFERENCE**


