AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Focus on Mucoadhesive Polymer Used in Nasal Drug Delivery System

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ABSTRACT

Medication activities might be enhanced by creating new medication conveyance frameworks; one such detailing being a mucoadhesive framework. These frameworks stay in close contact with the absorption tissue, the mucous layer, discharging the medication at the activity site prompting expanded bioavailability for both local and systemic impacts. Throughout the last few decades, the application of mucoadhesive polymers in nasal medication conveyance frameworks has picked up enthusiasm among pharmaceutical researchers as a method for advertising dose structure residence time in the nasal cavity and in addition for enhancing closeness of contact with absorptive membrane of the natural framework. Also, the upgraded paracellular absorption after the swelling of the mucoadhesive polymers on the nasal layers gives a critical path to the assimilation of the macromolecules through the nasal cavity. This review explained a few parts of mucoadhesion identified with the nasal medication conveyance framework. On the first check, the theories of the attachment of mucoadhesive polymers to the mucosa epithelium are described. Also, the attributes and application of a few generally utilized mucoadhesive polymers as a part of nasal medication conveyance are introduced. The mucoadhesive polymers have gigantic potential for the conveyance of therapeutic macromolecules, qualities, and immunizations through the nasal cavity with upgraded bioavailability.

Keywords: Mucoadhesion,Mucoadhesive polymers,Nasal medication,Absorption enhancers

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Received 20 November 2014, Accepted 28 November 2014

Please cite this article as: Pakhale BA *et al.*, Focus on Mucoadhesive Polymer Used in Nasal Drug Delivery System. American Journal of PharmTech Research 2014.

INTRODUCTION

Nasal organization offers an intriguing option for accomplishing systemic medication impacts to the parenteral course, which could be inconvenient or oral administration, which can bring about inadmissibly low plasma medication levels. Expectedly the nasal cavity is utilized for the treatment of local illnesses, for example, rhinitis and nasal blockage. However, in the past few decades, nasal drug delivery has been paid much more attention as a promising drug administration route for the systemic therapy.[1] This is because of the anatomy and physiology of the nasal cavity, for example, the huge surface area, profoundly vascularized epithelium, permeable endothelial layer, and the avoidance of first-pass metabolism[2.] Assessment of potential Merits[3] of mucoadhesive medication conveyance is laid out in underneath. Because of its ready accessibility, nasal medication organization has been considered as an option course for systemic utilization of medications limited to intravenous administration[4.]this is especially paramount for the conveyance of peptides and proteins that as of now are principally controlled through intravenous course due to their susceptibility to the gastrointestinal proteases[5]. Nasal medication conveyance can additionally give a course of passage to the cerebrum that circumvents the blood–brain barrier on the grounds that the olfactory receptor cells are in immediate contact with the central nervous system[6, 7] As of late, the nasal mucosa is considered as an alluring site for the conveyance of immunizations, not just in light of the fact that it has a moderately substantial absorptive surface and low proteolytic action, additionally on the grounds that, the nasal vaccines are patient compliant and diminish the generation expenses contrasted and the parenteral products. Extensive studies report that, when regulated intra nasally, immunizations can incite both local and systemic insusceptible reaction[8, 9] Regardless of the high penetrability of nasal membrane, for the most part, just little sub-atomic weight drugs (<1000 Da) show sufficient absorption in the nasal cavity[10] most hydrophilic and macromolecular medications, for example, insulin show low bioavailability or even no absorption at all[11.]the fundamental explanation behind this is that they are low permeable and susceptible to the proteases in the nasal mucosal layer, so these medications might be quickly cleared from the cavity, by ciliary development or enzymatic degradation before they achieve the circulation system, and can't cross the mucosal boundaries[12] Entrance enhancers, for example, surfactants[13] bile salts[14,15] fusidate subsidiaries[16], and phospholipids[17] have been utilized to enhance the medication absorption through nasal mucosa, yet toxicity tests have demonstrated that they were of restricted clinical use on account of their irreversible harm to nasal mucosa went accompanied with their absorption enhancing impacts[18.]somemucoadhesive polymers, for

example, cellulose, polyacrylates, starch, and chitosan, have turned out to be successful on enhancing intranasal absorption of hydrophilic macromolecules. These polymers attain this by expanding the medication retention time in the nasal cavity or enhancing intranasal retention; some of them can serve both the capacities. A large portion of these polymers are for the most part perceived as protected (GRAS) pharmaceutical excipients and not absorbed, so they would not be required to show systemic poisonous quality. Despite the fact that various difficulties are still to be succeeding, the empowering results animate pharmaceutical specialists to practice further endeavours to create new nasal details to supplant the ordinary parenteral products. In this article, the utilization of mucoadhesive polymers for the intranasal conveyance of medications is looked into. Their capacity of improving the intranasal absorption of macromolecular hydrophilic drugs will be focused on.

Meritis

- A delayed living arrangement time at the site of medication activity or absorption.
- A restriction of medication activity of the conveyance framework at a given target site.
- A build in the drug concentration gradient because of the extreme contact of molecule with the mucosal.
- An immediate contact with intestinal cells that is the first step before molecule retention.
- Ease of absorption.
- Termination of therapy is easy.{except gastrointestinal}
- Permits limitation of medication to the oral cavity for a delayed time of time.
- Can be directed to unconscious patients. {except gastrointestinal}
- Offers a great course, for the systemic conveyance of medications with high first pass metabolism, there by offering a more grater bioavailability.
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or antacid environment of digestive tract might be controlled by this course. E.g. buccal sublingual, vaginal.
- Drugs which indicate poor bioavailability by means of the oral course could be controlled advantageously.
- It offers a latent arrangement of medication absorption and does not require any enactment.
- The vicinity of salivation guarantees moderately substantial measure of water for medication dissolution dissimilar to if there should be an occurrence of rectal and transdermal courses.

- Systemic ingestion is quick.
- This course gives an option to the organization of different hormones, opiate, pain relieving, steroids, chemicals, cardiovascular executors and so forth.
- The buccal mucosa is much perfused with veins and offers a more grater penetrability than the skin.
- Less dosing recurrence.
- Shorter treatment period.
- Increased wellbeing edge of high strength medicates because of better control of plasma levels.
- Maximum use of medication enabling reduction in total amount of drug administered.
- Improved patient compliance and consistence because of less regular medication administration.
- Reduction in variance in consistent state levels and in this way better control of malady condition and diminished

Need of Mucoadhesive Drug Delivery System[19]

1. Controlled release of drugs.
2. Target & localized drug delivery.
3. By pass first pass metabolism.
4. Avoidance of drug degradation.
5. Prolonged effect.
6. High drug flux through the absorbing tissue.
7. Reduction in fluctuation of steady state plasma level.

Difference Between Mucoadhesion and Bioadhesion

The term‘bioadhesion’ define as ‘the attachment of a synthetic orbiological macromolecule to mucus and/or anepithelial surface for an extended period oftime’[20]. The term‘mucoadhesion ’define as ‘the binding of polymers tomucin/epithelial surface’[21]. In nasal drugdelivery, mucoadhesion means the adherence ofa polymeric material to nasal epithelial surface(bioadhesion) or nasal mucus (mucoadhesion).

Mucus Membrane

Mucus (or mucous) is tricky discharge created by, and coating, mucous membrane. Mucous membrane (mucosae) is the moist surfaces lining the walls of different body cavities, for example, gastrointestinal and respiratory tracts. They comprise of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist more often than not

by the vicinity of a mucus layer. Mucous layer of human living being is moderately porous and permits quick medication absorption.[22]. Mucus is thick colloid containing disinfectant catalysts, (for example, lysozyme) immunoglobulin's, inorganic salts, proteins, for example, lactoferrin and glycoproteins known as mucin that are delivered by globalt cells in the mucous layer. Mucin is the most critical glycoprotein of mucus and it's in charge of its structure. [23] Composition of mucus membrane explained in table 1.

Table 1: Composition of Mucus Layer[24]

Sr.no	Composition	%
1	Water	(95%)
2	Glycoprotein and lipids	(0.5-03%)
3	Mineral salts	(1%)
4	Free protein	(0.5-1%)

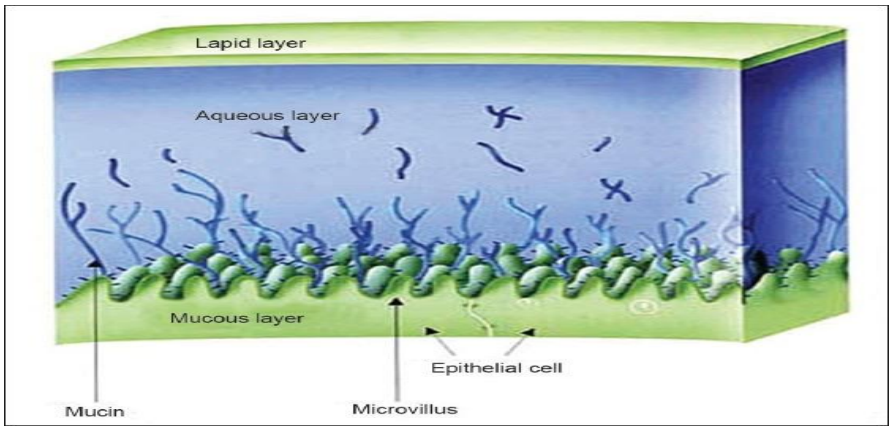

Figure 1: Structure of Mucus

Properties of Mucus Membrane

They are able to join together to make polymers or an extended three dimensional network i.e. gel[23]. The mucous site most used for drug administration and absorption is gastrointestinal but other routes also include nasal, oral, stomach, oesophagus, intestinal etc. Function of mucus membrane are explained in table 2

Table.2: Functions of Mucus Layer[25]

Sr.no	Function	Description
1	**Protective**	to protect against infectious agents such as fungi bacteria and viruses
2	**Barrier**	The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.
3	**Adhesion**	mucus has strong adhesion properties.
4	**Lubrication**	It is to keep the mucus membrane moist. Continuous secretion from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules

Sites for Mucoadhesive Drug Delivery Systems

The regular locales of use where mucoadhesive medication conveyance frameworks can conveyance pharmacologically active agent incorporate oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The current segment of the survey will give a review of a for mentioned conveyance sites.

Buccal cavity: The buccal cavity has an extremely restricted surface area of around 50 ^{cm2} however the simple access to the site makes it a favoured area for conveying dynamic active agent. The site gives a chance to convey pharmacologically dynamic active agent systemically by avoidance hepatic first-pass metabolism in addition to the local treatment of the oral injuries. The sublingual mucosa is moderately more penetrable than the buccal mucosa (because of the vicinity of substantial number of smooth muscle and fixed mucosa), henceforth details for sublingual conveyance are intended to discharge the dynamic operator rapidly while mucoadhesive definition is of imperativeness for the conveyance of dynamic active agent to the buccal mucosa where the dynamic active agent must be discharged in a controlled way. This makes the buccal cavity more suitable for mucoadhesive medication conveyance[26]

Nasal cavity: Like buccal cavity, nasal cavity likewise gives a potential site to the improvement of definitions where mucoadhesive polymers can assume a critical part. The nasal mucosal layer has a surface range of around 150-200 ^{cm2}. The retention time of a particulate matter in the nasal mucosa differs somewhere around 15 and 30 min, which have been attributed to the expanded movement of the mucociliary layer in the vicinity of outside particulate matter.[27]

Occular cavity: Ophthalmic mucoadhesive additionally is an alternate area of investment. Because of the nonstop development of tears and blinkering of eye lids there is a fast expulsion of the dynamic medicament from the visual depression, which brings about the poor bioavailability of the dynamic active agents. This might be minimized by delivering the medications and utilizing Occular inserts or patches.[28, 29, 30]

Viginal cavity & rectal cavity: The vaginal and the rectal lumen have likewise been investigated for the conveyance of the dynamic active agents both systemically and locally. The dynamic active agents implied for the systemic conveyance by this course of administration sidesteps the hepatic first-pass metabolism. Frequently the conveyance frameworks experience the ill effects of movement inside the vaginal/rectal lumen which may influence the conveyance of the dynamic active agent to the particular area.[31, 32, 33]

GIT tract: Gastrointestinal tract is likewise a potential site which has been investigated since long for the advancement of mucoadhesive based details. The adjustment of the transit time of the

conveyance frameworks in a specific area of the gastrointestinal framework by utilizing mucoadhesive polymers has created much enthusiasm among scientists around world.[34]

The Mucoadhesive / Mucosa Interaction

- **Chemical bonds**

For adhesion to occur, molecules must bond across the interface. These bonding can occurby following way.[35]

a. **Ionic bonds**—where two oppositely charged ions attract each other via electrostatic interaction form a strong bond (e.g. in a salt crystal).
b. **Covalent bonds**—where electrons are shared, in pairs, between the bonded atoms in order to 'fill' the orbitals in both. These are also strong bonds.
c. **Hydrogen bonds**—here a hydrogen atom, when covalently bond as oxygen, fluorine or nitrogen, carries a slight positively charge and is therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.
d. **Van-der-Waals bonds**—these are some of the weakest forms of interaction that arise from dipole dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non- polar substances.
e. **Hydrophobic bonds**—more accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non present in an aqueous solution. Water molecules adjacent to non- bonded structures, which lower the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect.

Mucoadhesion Theories[36, 37]

It is accounted for that, in spite of the fact that the synthetic and physical premise of mucoadhesion are not yet well seen there are six traditional theories adapted from studies on the execution of a few materials and polymer adhesion which clarify the phenomenon. Contact angle and time assumes a real part in mucoadhesion.

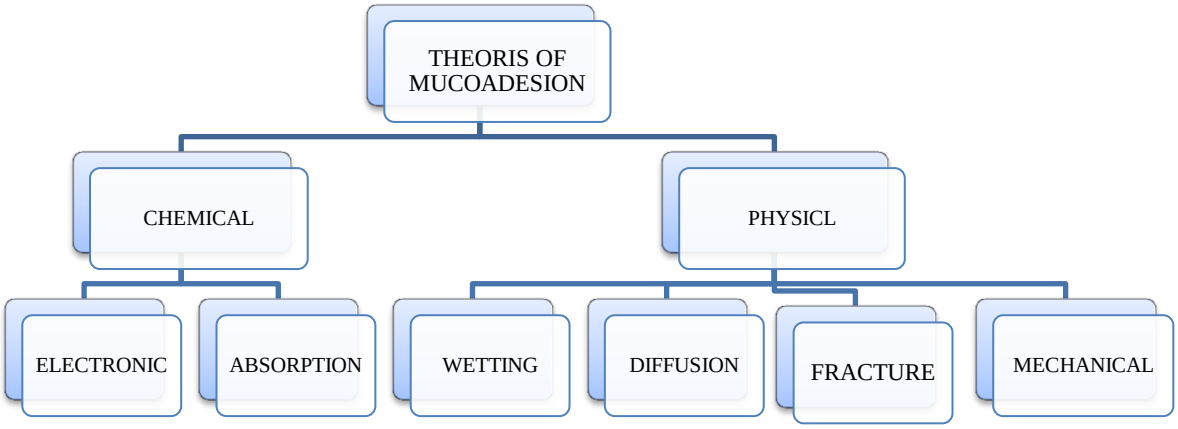

Figure-1:

1. **Electronic theory**: Electronic theory is focused around the introduce that both mucoadhesive and organic materials have restricting electrical charges. Hence, when both materials come into contact, they exchange electrons prompting the building of a twofold electronic layer at the interface, where the attractive forces inside this electronic twofold layer decides the mucoadhesive quality.

2. **Adsorption theory**: According to the adsorption theory, the mucoadhesive devise sticks to the mucus by auxiliary concoction associations, for example, in Van der Waals and hydrogen bonds, electrostatic attractions or hydrophobic interactions. Case in point, hydrogen bonds is the predominant interfacial force in polymers containing carboxyl groups. Such forces have been viewed as the most essential in the adhesive interactions phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion.

3. **Wetting theory:** The wetting theory applies to fluid system which exhibit affinity to the surface to spread over it. This affinity could be found by utilizing measuring procedures, for example, the contact angle. The general principle expresses that the bring down the contact angle then the more prominent affinity (Figure 2). The contact angle should to be equivalent or near zero to give sufficient spreadability.

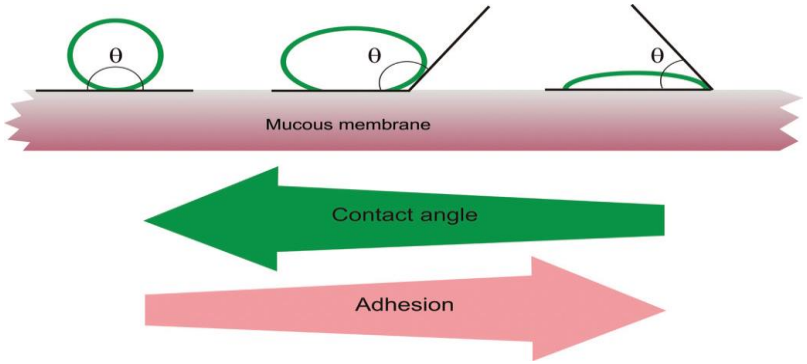

Figure 2: Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion

4. Diffusion theory: Diffusion theory applicable to the interpenetration of both polymer and mucin binds to a sufficient depth to make a semi-permanent adhesive bond. It is accepted that the adhesion force builds with the level of penetration of the polymer chains. This penetration rate relies on upon the diffusion coefficient, flexibility and nature of the mucoadhesive chains, portability and contact time. The adhesion quality for a polymer is arrived at when the depth of penetration is approximately equivalent to the polymer chain size. In order fordiffusion to occur, it is important that the components involved have good mutual solubility, that is, boththe bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, thebetter the mucoadhesive bond.

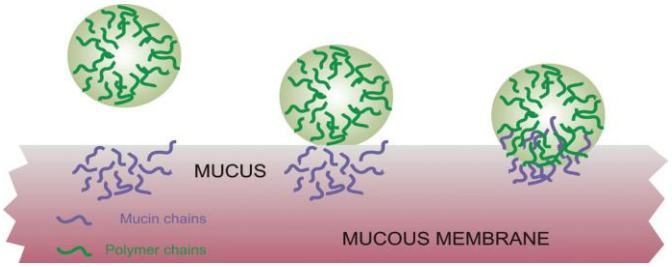

Figure 3: Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus.

5. Fracture theory: This is maybe the most-utilized theory within studies on the mechanical estimation of mucoadhesion. It analyses down the force needed to divide two surfaces after adhesion is built (Figure 4). This force, sm, is frequently figured in tests of resistance to rupture by the proportion of the maximal detachment force, Fm, and total surface area, A0, included in adhesive interactions (equation1):

$$Sm = Fm / Ao \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots [1]$$

Since the fracture theory is concerned just with the force needed to particular the parts, it doesn't consider the interpenetration or diffusion of polymer chains. Therefore, it is proper for utilization in the calculations for inflexible or semi-rigid bioadhesive materials, in which the polymer chains don't enter into the mucus layer.

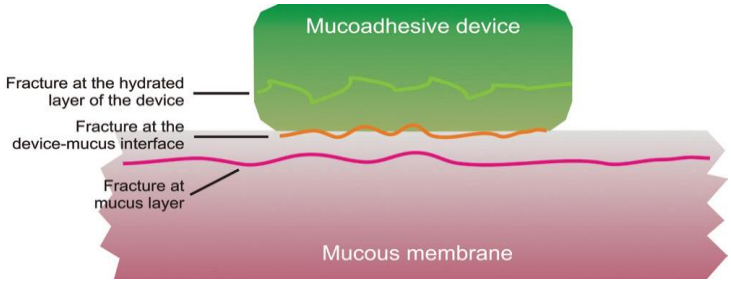

Figure 4: Regions where the mucoadhesive bond rupture can occur.

6. Mechanical theory: Mechanical theory considers bond to be because of the filling of the irregularities on a harsh surface by a mucoadhesive fluid. In addition, such harshness expands the interfacial range accessible to connections there by helping scattering vitality and could be viewed as the most essential wonder of the methodology. Lee, Park, Robinson, 2000 had portrayed that it is improbable that the mucoadhesion procedure is the same for all cases and along these lines it can't be depicted by a solitary hypothesis. Indeed, all speculations are pertinent to recognize the essential procedure variables. The systems representing mucoadhesion are likewise controlled by the inherent properties of the formulation and by environments domain in which it is connected. Inherent components of the polymer are identified with its atomic weight, concentrations and chain flexibility. For liner polymers, mucoadhesion expands with atomic weight, however the same relationship does not hold for non-liner polymers. It has been demonstrated that more focused mucoadhesive dispersion are held on the mucous film for more periods, as on account of frameworks structured by in situ gelification. After application, such frameworks spread effortlessly, since they display rheological properties of a fluid, yet incredibly into contact the absorption site, along these lines keeping their fast evacuation. Fasten flexibility is basic to merge the interpenetration between of formulation and mucus. The earth related variables incorporate pH, starting contact time, swelling and physiological varieties. The pH can impact the creation of ionisable gatherings in polymers and the formation of charges on the mucus surface. Contact time in the middle of mucoadhesive and mucus layer decides the degree of chain interpenetration. Super-hydration of the framework can prompt develop of adhesive without adhesion. The thickness of the mucus layer can differ from 50 to 450 µm in the stomach to short of what 1µm in the oral cavity. Other physiological varieties can additionally happen with illness.

Mechanism of Mucoadhesion

The methodology of mucoadhesion after nasal administration identifies with the interaction between the mucoadhesive polymer and the mucus secreted by the sub-mucosal glands.[38] The successive occasions that happen amid the mucoadhesion incorporate the best possible wetting and

swelling of the polymer, and intimate contact between the polymer and the nasal mucosa. At that point, the swelled mucoadhesive polymer infiltrates into the tissue fissure emulated by the interpenetration between the polymer chains and protein chains of the mucus [figure 1]. To get sufficient absorption of medications, to start with, the formulation spread well on the nasal mucosa. Hence, the spreadability is extremely essential for the liquid mucoadhesive formulation, so do the flowability and wettability for the solid mucoadhesive formulation[39] Hydration of the polymer (swelling) assumes an extremely vital part in mucoadhesion, through which the polymer chains are liberatedand collaborate with the biological tissue.[40] During hydration, there is a separation of hydrogen bond of the polymer chains. At the point when the polymer–water interaction gets to be more prominent than the polymer–polymer interaction, satisfactory free polymer chains will be accessible for interaction between the polymer and biological tissue. There is a critical degree level of hydration needed for ideal mucoadhesion. The deficient hydration because of the absence of the water prompts fragmented liberation of the polymer chains. Then again, an extreme measure of water will weaken the mucoadhesive bonds by over diluting the polymer solution.[41] The polymer chains penetrating into the tissue crevices can keep down the ciliary development, which will expand the retention time of the medications in the nasal cavity. Moreover, the presence of the mucoadhesive carrier likewise reduces the contact between the medications and the enzyme existing in the mucosa. These both can improve the intranasal assimilation of hydrophilic medication. Separated from these, the lack of hydration of the epithelial cells after hydration might likewise briefly open the tight intersections between the epithelial cells and enhance the paracellular absorption of macromolecular medications. This capacity of the mucoadhesive polymer is exceptionally vital for the improvement of the intranasal absorption of macromolecules weighting over 1000 Da.[42] Mucoadhesion can ease off the mucociliary clearance, yet with time, mucus creation will prompt the over the top swelling of the mucoadhesive polymer and the reduction of the mucoadhesion security quality, permitting a recuperation of ordinary mucociliary development rate and the bond strength of the polymer from the mucosa. Although numerous references demonstrate that the mucoadhesive polymer are compelling on improving the intranasal retention of macromolecular medications, not very many papers concentrate on the progressions of gel structure and rheology of the mucus brought on by the mucoadhesive polymer, to what degree the cooperation between the polymer and the mucus impacts the arrival of the medications incorporating in the disease condition. Disease conditions can influence mucoadhesion because of their impact on either bodily fluid generation or ciliary movement, and after that may bring about undesired medication discharge. In this manner, a great understanding

of the way of mucus in these diseases is basic in outlining a good nasal medication delivery. Mucoadhesive capacities of polymers should be mulled over under such disease conditions amid the product development.

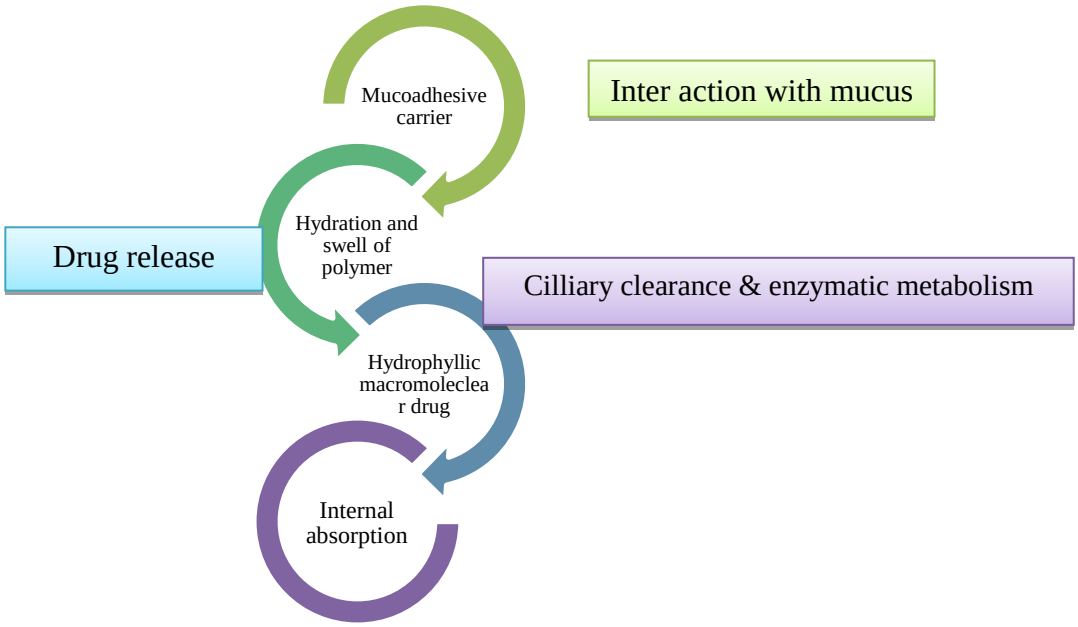

Figure 5: Schemated of the mucoadhesive internal drug delivery system

Factors Affecting Mucoadhesion[43, 44]

The Mucoadhesive power of polymer is affected by the nature of polymer and also by the nature of surrounding media.

They are following:-

1. Polymer related factors

a) Molecular weight
b) Concentration of active polymer
c) Flexibility of polymer chains
d) Special conformation
e) Swelling

2. Environmental related factors

a) PH of polymer substrate interface
b) Applied strength
c) Initial contact time

3. Physiological factors

a) Mucin turnover
b) Disease state

1. Polymer related factors

i) **Molecular weight**: Numerous studies have demonstrated that there is a sure molecular weight at which bio adhesion is at a greatest. The interpenetration of polymer particle is good for low molecular weight polymers while developments are favoured for high molecular weight polymers.

ii) **Flexibility of Polymer chains:** As water solublet polymers get to be cross-linked, the mobilitybility of the individual polymer chain diminishes. As the cross-linking thickness builds, the compelling length of the chain which can enter into the mucus layer reductions significantly further and mucoadhesive quality is reduced.

iii) **Spatial confirmation:** Besides molecular weight or chain length, spatial adaptation of a particle is additionally important. The helical confermation of dextran may shield a lot of people adhesively dynamic gatherings fundamentally in charge of attachment, dissimilar to PEG polymers which have liner confermation.

2. Environment Related Factors

i) pH: pH was also found to have a significant impact on mucoadhesion as observed in investigations of Polyacrylic polymers cross-linked with -COOH bunches. pH influences the charge on the surface of both mucus and the polymers. Mucus will have an alternate charge thickness, contingent upon pH, in view of contrasts in separation of useful gatherings on the starch moiety and amino acids of the polypeptide spine. Most extreme grip was seen at pH 5 and 6 and least at pH 7.

ii) Applied Strength: To place a solid bioadhesive framework, it is important to apply a characterized quality. The adhesion strength builds with the connected quality or with the duration of its application, up to an ideal. On the off chance that high pressure is applied a sufficiently long time of time, polymers get to be mucoadhesive despite the fact that they don't have appealing interaction with mucin.

iii) Initial contact time: The introductory contact time in the between of mucoadhesives and the mucus layer decides the degree of swelling and the interpenetrations of polymer chains. Alongside the beginning pressure, the starting contact time can significantly influence the performance of a system. . The mucoadhesive strength builds as the starting contact time expands.

iv) Degree of Hydration: Depending on the level of hydration bond properties will be distinctive. It is greatest at a certain level of hydration. At the point when the level of hydration is high, adhesiveness is lost likely because of arrangement of tricky, non-adhesive mucilage in an environment of large amount of water at or close to the Interface.

3. Physiological Variables:[45-47]

i)Mucin Turnover: The regular turnover of mucin particles from the mucus layer is vital for least two reasons. First and foremost, the mucin turnover is required to limit the residence time of the mucoadhesive on the mucus layer. Regardless of how high the mucoadhesive strength is. Mucoadhesives are withdrawn from the surface because of mucin turnover. The turnover rate may be diverse in the vicinity of mucoadhesive. Second, mucin turnover brings about considerable measure of dissolvable mucin atoms. These atoms connect with mucoadhesives before they have an opportunity to interface with mucus layer. Mucin turnover may rely on upon alternate variables, for example, vicinity of blood. Lehr et al. (1991) figured mucin turnover time of 47-270 minutes. The ciliated cells in the nasal cavity are known to transport the mucus to the throat at a rate of 5mm/min. the mucociliary clearance in the tracheal region has been discovered to be in the scope of 4-10mm/min.

ii) Disease States: Physicochemical properties of mucus are known to change during disease states, for example, regular cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and parasitic contaminations of the female conceptive tract and inflammatory states of the eye. The definite structural progressions occurring in mucus under these conditions are not clearly understood. If mucoadhesives are to be utilized within the diseased state express, the mucoadhesive property needs to be assessed under it.

Mucoadhesive Polymers[48]

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable systems, jointed by cross-interfacing agent. These polymers have ideal extremity to verify that they allow sufficient wetting by the mucus and ideal smoothness that allows the common adsorption and interpenetration of polymer and mucus to happen. Mucoadhesive polymers that adhere to the mucin-epithelial surface might be advantageously isolated into three wide classes:

1. Polymers that get to be sticky when put in water and owe their mucoadhesion to stickiness.
2. Polymers that follow through nonspecific, non-covalent communications that is basically electrostatic in nature (in spite of the fact that hydrogen and hydrophobic holding may be huge).
3. Polymers that tie to particular receptor site on tile surface toward oneself. Each of the three polymer sorts could be utilized for medication conveyance.

Ideal Mucoadhesive Polymer Characteristics

A mucoadhesion promoting agent or the polymer is added to the formulation which serves to promote the following of the dynamic pharmaceutical element to the mucosa. The agent can have such extra properties like swelling to promote the disintegration when in contact with the

salivation. As under stood, that different physical and chemical compound trades can influence the polymer/mucus adhesion, so as polymer should be precisely chosen on account of the accompanying properties.[49]

1. Polymer must have a high atomic weight up to 100.00 or more this is important to advertise the adhesiveness between the polymer and mucus.[49]

2. Long chain polymers-chain length must be long enough to push the interpenetration and it should not be excessively long that diffusion turns into an issue.[50]

3. High thickness.

4. Level of cross interfacing it impacts bind versatility and imperviousness to disintegration. Exceedingly cross linked polymers swell in vicinity of water and hold their structure. Swelling favours controlled arrival of the medication and expands the polymer/mucus interpenetration. Yet as the cross interfacing expands, the chain portability diminishes which decreases the mucoadhesive quality.[50]

5. Spatial compliance.

6. Adaptability of polymer chain- this pushes the interpenetration of the polymer inside the bodily fluid system.[51]

7. Concentration of the polymer- an ideal optimization is required to promote the mucoadhesive quality. It depends in any case; on the solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi-solid dosage forms an optimum concentration essential beyond which the adhesive strength decreases.[52]

8. Ideal hydration- excessive hydration prompts diminished mucoadhesive quality because of structuring of slippery mucilage.[53- 55]

9. Ideal pH – mucoadhesion is ideal at low pH conditions however at pH conditions yet at higher pH values a change in the conformity happens into a pole like structure making them more accessible for entomb dispersion and interpenetration.[56] At exceptionally lifted pH values, emphatically charged polymers like chitosan structure polyelectrolyte edifices with mucus and display solid mucoadhesive strengths.

10. High appliedstrength and initial contact time.

11. It should nontoxic, economical, biocompatible ideally biodegradable.[57]

Molecular Characteristics

Examinations concerning polymers with different molecular attributes directed by numerous creators[58] have prompted various conclusions in regards to the molecular qualities needed for

mucoadhesion. The properties displayed by a decent mucoadhesive may be condensed as takes after[59]

1. Solid hydrogen holding groups (-OH, - COOH).

2. Solid anionic charges.

3. Sufficient adaptability to enter the mucus system or tissue fissure.

4. Surface strain qualities suitable for wetting mucus /mucosal tissue surface.

5. High sub-atomic weight. Despite the fact that an anionic nature is ideal for a decent mucoadhesive, a scope of nonionicmolecules (e.g., cellulose subsidiaries) and a few cationics (e.g., Chitosan) might be effectively utilize.

Classification Of Mucoadhesive Polymers

The polymers can be classified based on source **(Table 3),** solubility **(Table 4),** charge **(Table 5) and** bioadhesive forces **(Table 6**), mucoadhesive force **(Table 7),** mucoadhesive potential **(Table 8),**

Table 3: Classification of polymers based on source.

Natural Polymers	**Synthetic Polymers**
i. Agarose	**Polymers based on poly(meth)acrylic acid.**
ii. Chitosan	i. Carbopol
iii. Gelatin	ii. Polycarbophil
iv. Hyaluronic acid	iii. Polyacrylic acid
v. Carrageenan	iv. Polyacrylates
vi. Pectin	v. Copolymer of acrylic acid
vii. Sodium alginate.	vi. Polyethylene glycol
Cellulose derivatives	vii. Copolymer of methylvinyl ether and
i. Carboxy methyl cellulose.	viii. Methacrylic acid
ii. Thiolated Carboxy methyl cellulose	ix. Poly-2-hydroxyethylmethacrylate
iii. Sodium Carboxy methyl cellulose	x. Copolymer of acrylic acid and
iv. Hydroxyethylcellulose,	xi. Ethylhexylacrylate
v. Hydroxypropylcellulose,	xii. Polymethacrylate
vi. Hydroxypropylmethylcellulose	xiii. Polyalkylcyanoacrylates
vii. Methylcellulose	xiv. Polyisobutylcyanoacrylate
viii. Methylhydroxyethylcellulose	xv. Polyisohexylcyanoacrylate
	Others
	i. Poly-N-2-hydroxypropylmethacrylamide Polyhydroxyethylene
	ii. Poly vinyl alcohol
	iii. Poly vinyl pyrrolidine
	iv. Thiolated polymers

Table 4: Classification of polymers based on aqueous solubility.

Water Soluble Polymers	**Water Insoluble Polymers**
Cellulose derivatives	**Polymers based on poly(meth)acrylic acid**

i. Carboxy methyl cellulose
ii. Thiolated Carboxy methyl cellulose
iii. Sodium Carboxy methyl cellulose
iv. Hydroxyethylcellulose
v. Hydroxypropylcellulose
vi. Hydroxy propyl methyl cellulose
vii. Methylcellulose
viii. Methylhydroxyethylcellulose

Others

i. Poly-N-2-hydroxypropylmethacrylamide
ii. Polyhydroxyethylene
iii. Poly vinyl alcohol
iv. Poly vinyl pyrrolidine
v. Thiolated polymers.
vi. Ethyl cellulose
i. Carbopol
ii. Polycarbophil
iii. Polyacrylic acid
iv. Polyacrylates
v. Copolymer of acrylic acid
vi. PEG
vii. Copolymer of methyl vinyl ether
viii. Methacrylic acid
ix. Poly-2-hydroxyethylmethacrylate
x. Copolymer of acrylic acid and
xi. Ethylhexylacrylate
xii. Polymethacrylate
xiii. Polyalkylcyanoacrylates
xiv. Polyisobutylcyanoacrylate
xv. Polyisohexylcyanoacrylate

Table 5: Classification of polymers based on charge.

Cationic Polymers	Anionic Polymers	Non-ionic Polymers
i. Aminodextran	i. Carboxy methyl cellulose	i. Hydroxy ethyl starch
ii. Chitosan	ii. Pectin	ii. Hydroxy propyl cellulose
	iii. Carbopol	iii. Polyethylene glycol,
	iv. Polyacrylates	iv. Polyvinyl alcohol,
		v. Polyvinylpyrrolidine
		vi. Eudragit- NE30D

Table 6: Classification of polymers based on bioadhesive forces

Covalent Bonds	Electrostatic Interactions	Hydrogen Bonds
i. Cyanoacrylate	**i.** Chitosan	i. Acrylates
		ii. Carbopol
		iii. Polycarbophil
		iv. Polyvinyl alcohol

Table 7: Order of mucoadhesive force for various polymers [63, 64]

Mucoadhesive Polymers	Mean Adhesive Force (%) with Standard Deviation
Poly(acrylic acid)	185.0 ±10.3
Tragacanth	154.4 ±7.5
Poly(methylvinylether comaleic anhydride)	147.7 ±9.7
Poly(ethylene oxide)	128.6 ±4.0
Methylcellulose	128.0 ±2.4
Sodium alginate	126.2 ±12.0
Hydroxypropylmethyl cellulose	125.2 ±16.7
Karaya gum	125.2 ±4.8
Methyl ethyl cellulose	117.4 ±4.2
Soluble starch	117.2 ±3.1
Gelatin	115.8 ±5.6
Pectin	100.0 ±2.4
Poly (vinyl pyrrolidone)	97.6 ±3.9

Poly (ethylene glycol)	96.0 ± 7.6
Poly (vinyl alcohol)	94.8 ±4.4
Hydroxypropylcellulose	87.1 ±13.3

Table.8: Relative mucoadhesive performance of some potential mucoadhesive pharmaceutical polymers [66, 67]

Polymer	Bioadhesive Property
Carboxy methyl cellulose	+++
Hydroxy propyl methyl cellulose	+++
Carbopol 934	+++
Tragacanth	+++
Sodium alginate	+++
Polycarbophil	+++
Hydroxy ethyl cellulose	+++
Gelatin	++
Guar gum	++
Gum karaya	++
Pectin	+
Acacia	+
Polyvinyl pyrrolidone	+

Depending upon source[60, 61]

A. Natural Polymers

B. Synthetic Polymers

Depending upon aqueous solubility[62, 63]

A. Water Soluble

B. Water insoluble

Depending upon charge[64, 65]

A. Cationic polymers

B. Anionic polymers

C. Nonionic polymers

Depending upon potential bioadhesive forces[61]

A. Covalent Bonds.

B. Electrostatic Interactions.

C. Hydrogen Bond

Mucoadhesive Polymers Used In Nasal Drug Delivery

1] Cellulose Derivatives

There are many pharmaceutical grade derivatives of cellulose widely used in different administration routes. Several cellulose derivatives have proved to be effective on enhancing the intranasal absorption of drugs, including soluble cellulose derivatives such as hydroxypropyl

methylcellulose, hydroxypropyl cellulose (HPC), methylcellulose (MC), and carboxymethyl cellulose (CMC), and insoluble cellulose derivatives such as ethylcellulose and microcrystalline cellulose (MCC). Cellulose derivatives can markedly prolong the residence `time of drugs in the nasal cavity due to their desirable mucoadhesive property[68] Additionally, due to their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs[69] For these reasons, using celluloses as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective on increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs [Table 9]. For example, administered nasally with CMC, apomorphine can obtain a relative bioavailability of 102% compared with subcutaneous injection in rabbits[70] Another study reported that an absolute bioavailability up to 90.77% could be achieved for ketorolac tromethamine administered with MCC[71].The peptide drugs, leuprolide and FD-4, when dosed with MCC/HPC through nasal route, reached an absolute bioavailability of 34.9% and 35.5% in rabbits, respectively[72]. Sometimes, combination of the celluloses with other absorption enhancer would obtain the better effectiveness than using the polymer alone[73] reported that the intranasal absolute bioavailability of ciprofloxacin in rabbits using MC and HEC alone as enhancer is only 18.2% and 19.46%, respectively. When combining with the Tween 80, the bioavailability increased to 22.35% and 25.39%, respectively.[74] In another study by on the intranasal delivery of dopamine, the combination of the HPC and azone leaded to an absolute bioavailability of almost 100%, while it was only 25% for using HPC alone.[73]

Table 9: Summary of some nasal drug delivery studies where cellulose derivatives were employed

Mucoadhesive Polymer	Drug	Dosage Form	Reference
CMC	Apomorphine	Powder	Ugwoke Mi *et al*.[70]
MCC	Ketorolac Acid	Spray	Quadir M *et al*.[71]
HPC	Dopamine	Liquid	Ikeda K *et al*.[74]
HPC	Metaclopramide	Gel	Zaki Nm *et al*.[68]

2] Polyacrylates

Polyacrylates have been investigated very frequently in many drug administration routes, like nasal drug delivery systems, due to their excellent mucoadhesive and gel-forming capability. Among the pharmaceutical polyacrylates, carbomers, and Polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in the nasal mucoadhesive drug delivery systems.[75] Polyacrylates, capable of attaching to mucosal surfaces, can offer the prospects of prolonging the residence time of drugs at the sites of drug absorption, and ensure intimate contact between the

formulation and membrane surface. Studies by Ugwoke *et al*. in rabbits reported that the use of Carbopol 971P in nasal dosage forms increases their residence time in the nasal cavity. The percentage of the formulations cleared from the nasal cavity at 3 hours was 24% for Carbopol 971P, while it was 70% for lactose. Sustained release of drugs can also be obtained by using polyacrylates in nasal formulation, which result in a more stable blood concentration-time curve. Table 2 shows the use of polyacrylates in nasal drug delivery system[70,76] Another research by Ugwoke *et al*. showed that the Tmax of the Carbopol 971P-containing formulation of apomorphine was 52.21 minutes, which represented a 5-fold improvement compared with that of the lactose-containing formulation, while the Cmax of the Carbopol 971P-containing formulation was 330.2 ng/ml, lower than that of the lactose-containing formulation, which was 450.7 ng/ml.[70,77] Besides the mucoadhesion capability, polyacrylates may also temporarily open the tight junctions between the epithelial cells during the swelling progress in the nasal cavity and improve the paracellular absorption of drugs.[78] An absolute bioavailability of 14.4% in rabbits was reported for intranasal insulin formulation containing Carbopol 974P. Callens and Remon reported that the effect of Carbopol on the mucosa is negligible and reversible; no change of the epithelium barrier was observed even after a 4-week administration of Carbopol-based powder formulation in rabbits.

Table 10: Summary of the studies on the use of polyacrylates in nasal drug delivery

Mucoadhesive Polymer	Drug	Dosage Forms	Reference
Carbopol 971P	Apomorphine	Powder	Ugwoke MI *et al*.[70]
Carbopol 981P/Dm B-CD	Metadopramide	Powder	Quadir M *et al*.[80]
Carbopol 934/HPC	Metadopramide	Powder	Callens C *et al*.[78]

3] Starch

The starch is one of the most widely used mucoadhesive carrier for nasal drug delivery, which has been reported to be effective on improving the absorption of both small hydrophobic drugs and hydrophilic macromolecular drugs **[Table 11**]. Maize starch is the most preferred class for pharmaceutical purpose, among which the drum-dried waxy maize starch, due to its better bioadhesive property, has been considered as the best one compared with starch processed through other methods.[79] Starch can be used as nasal drug carriers in the form of powder microspheres nanoparticles [Table 11] among which the degradable starch microspheres (DSM), also known as SpherexR, is the most widely used and also the first example of mucoadhesive microparticulate nasal delivery system. These microspheres are prepared by an emulsion polymerization technique, in which the starch is cross-linkedwith epichlorohydrin and can incorporate molecules weighting less than 30 kDa[80] have observed that the half-life of clearance for DSM was prolonged to 240 minutes as compared with 15 minutes for the liquid and powder control formulations.[81]

4] Chitosan

Chitosan [2-amino-2-deoxy-(1→4)-β-d-glucopyranan] isa linear cationic polysaccharide which is obtained by a process of deacetylation from chitin, an abundant structural polysaccharide in shells of crustacea, such as lobsters, shrimps, and crabs. Due to the NH2 groups resultant from the deacetylation process, chitosan is insoluble at neutral and alkaline pH. However, it can form water-soluble salts with inorganic and organic acids including glutamic acid, hydrochloric acid, lactic acid, and acetic acid. Toxicity tests have revealed that the LD50 of chitosan in mice exceeds 16 g/kg (Paul and Garside, 2000). Because of its low cost, biodegradability, and biocompatibility, chitosan has been increasingly applied as pharmaceutical excipients in oral, ocular, nasal, implant, parenteral, and transdermal drug delivery.[82]Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption due to their excellent mucoadhesive properties. It was also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces[83] **Table 12** shows various chitosan derivatives used in nasal drug delivery system. Soane *et al*. reported that chitosan microspheres and solutions resulted in three- and eight-fold longer clearance half-lives compared with sodium pertechnetate solution in sheep nasal cavity, respectively[84]. In addition, many studies have proved that chitosan and its derivatives could transiently open the tight junctions between the cells and lead to the paracellular transport of drugs[85] and Chung*et al*. has observed interpenetration of thermo-sensitive gels of insulin in nasal delivery by cross linking of chitosan. The preparation shows sustained release of insulin and improved pharmacological efficiency.[86]Chemical and biological properties of chitosan, such as mucoadhesion and ability in enhancing nasal absorption, are determined by the types of derivatives, degree of deacetylation, and molecular weight, because chitosan is only soluble in acidic environment in which the amino groups at the C-2 position are protonated. At neutral pH, most chitosan molecules will lose their charge and precipitate from solution[86]. Recent studies have shown that only protonated, soluble chitosan can trigger the opening of tight junctions and there by facilitate the paracellular transport of hydrophilic mannitol[87]. To improve the poor water solubility of chitosan, some derivatives were synthesized, such as trimethyl chitosan.[88]Thanou *et al*. reported that the trimethyl chitosan was soluble and effective on enhancing intranasal absorption even at neutral pH.[88] N-trimethyl chitosan hydrochlorides are more mucoadhesive than unmodified chitosans and show a higher bioavailability *in vivo* compared with the unmodified chitosans.[89] Mei *et al*. reported that the permeation-enhancing effect ofchitosan increased with increasing molecular weight up to Mw 100.[90], Zaki *et al*. found that there is no significant difference between the constants of intranasal absorption for metoclopramide HCl administered with chitosan high weight

(600 kDa) and low weight (150 kDa) even though they differ in molecular weight by four-fold. Due to the positive charge of chitosan in a weak acidic environment, it can also be applied to deliver the negatively charged DNA through nasal mucosa and protect them from nuclease degradation.[70]Compared with viral vectors, this alternative vector markedly reduced the safety risks that meanwhile result in high transfectability. Recently, many studies show that nasal immunization with chitosan plus inactive vaccine is a potentially effective, easily administered form of vaccination[91]. *Bordetella pertussis* filamentous hemagglutinin and recombinant pertussis toxin have shown to induce very strong systemic and mucosal immune reactions against the antigens when intranasal administrated with chitosan.[92]Bacon *et al*. have reported that chitosan solutions are able to enhance both the mucosal and systemic immune responses against influenza virus vaccines. Only in mice which received chitosan/vaccine formulation intranasal, high IgA titers in nasal washings could be found. This was not observed in mice receiving the antigen through subcutaneous injection.[93]

Table 11: Summary of some nasal drug delivery studies where starch and other carbohydrates were employed

Mucoadhesive Polymers	Drug	Dosage Forms	Reference
DSM	Apomorphine	Powder	Ugwoke MI *et al*.[70]
DSM/STDHF	Gentamycine	Powder	Illum L *et al*. [81]
DDMW	Hgs	Powder	Illum L *et al*. [81]

Table 12: Summary of some nasal drug delivery studies where chitosan were employed

Mucoadhesive Polymer	Drug	Dosage Form	Reference
Chitosan	Tetramethyl Pyrazosine	Liquid	Mei D *et al*. [91]
Chitosan	Insulin	Liquid	Illum L *et al*. [82]
Chitosan	Metaclopromide	Liquid	Zaki N M *et al*. [68]

Techniques to Evaluate Mucoadhesion[94]

***1. In vitro* methods**

- Tensile strength measurement.
- Shear strength measurement.
- Modified physical balance.
- Detachment force method.
- Microbalance method.
- Ex-vivo mucoadhesion.
- Falling film method.
- Swelling index.

- Wash off method.
- Colloidal gold staining.
- Adhesion number.
- Viscometric method.
- Everted sac technique.
- Drug permeation.
- Fluorescent probe method.
- Mucoadhesion time.
- Surface pH study.
- Scanning Electron microscopy. (SEM)
- Novel Rheological Approach.
- Texture analyzer.

2. ***In vivo* methods:**

- Use of radioisotopes.
- Use of gamma scintigraphy.
- X-ray studies
- In vivo evaluation of mucoadhesive studies
- Isolated loop technique.

3. ***In vitro* as well as *in vivo* method:**

- Biacore (Surface Plasmon Resonance)

CONCLUSION

Mucoadhesive medication conveyance frameworks have a high capability of being valuable method for conveying medications to the body, maybe especially for topical or local administration where the mechanical trauma accomplished by the measurements structure may be minimized. Mucoadhesive frameworks are known to give intimate contact between measurement structure and the absorptive mucosa, coming about accordingly in a high medication flux through the engrossing tissue. Current utilization of mucoadhesive polymers to build contact time for a wide mixed bag of medications and courses of organization has demonstrated emotional change in both particular helps and more general patient agreeability. Mucoadhesive polymers may give a important tool to enhance the bioavailability of the dynamic executor by enhancing the living arrangement time at the conveyance site. It is a development region whose objective is the improvement of new gadgets and then some "intelligent" polymers, and in addition the production

of new techniques that can better illustrate the mucoadhesion sensation. With the incredible increase of new particles originating from medication research, mucoadhesive frameworks may assume an expanding part in the improvement of new pharmaceuticals. The mucoadhesive medication conveyance framework will keep on appealing to both pharmaceutical scientists and the pharmaceutical business.

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