

**Novel polymers for mucoadhesive drug delivery**

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***Corresponding author e-mail:** abdulmalikluck@gmail.com**ABSTRACT**

The purpose of current article focuses on polymers used in mucoadhesive drug delivery system. The term “mucoadhesive” is defined as the “attachment of drug elongated with suitable carrier like natural or synthetic polymer to mucus and/or an epithelial surface”. It is a popular novel drug delivery system because relatively permeable of mucous membranes, and mucus have higher blood flow therefore allowing rapidly uptake of a drug into the systemic circulation. It avoid the first pass metabolism. Mucoadhesive polymers are used in various dosage forms to obtain systemic delivery of therapeutics agent through the different mucosa. The dosage forms which involve in mucoadhesive drug delivery system are tablets, semisolid patches, powders, tapes and films. The mucoadhesive polymers which are used in various dosage form are PEG, Tragacanth, Guar gum, HPMC, MC, sodium CMC, CMC and Sodium alginate etc. and having mucoadhesive property. The ideal characteristics of a mucoadhesive polymer matrix is to adhere rapidly to the mucosal layer without causing any change in the physical property of the delivery matrix. The matrix have minimum interference to the release of the therapeutic agent and should be biodegradable without producing any toxic byproducts. The polymer matrix have a capability to inhibit the enzymes which is present at the delivery site and enhance the penetration of the therapeutics agent. The objective of this review article is to design improved drug delivery systems and to study about the novel mucoadhesive polymers used in mucoadhesive drug delivery system.

Keywords: Mucoadhesion, Mucoadhesive mechanism, Mucoadhesive polymers, chitosan and guar gum, Drug delivery system.

INTRODUCTION

Mucoadhesion process is a complex process involves in the polymeric drug delivery system. The mucoadhesion process which involve in the polymeric drug delivery system such as adsorption, wetting, chemical bonding etc. Mucoadhesion process is mainly influenced by polymeric based properties like degree of cross linking, chain length, and various functional groups in polymer structure. Mucoadhesive systems have widely used throughout many mucosal covered organelles for active ingredients delivery for local or systemic effect. The concept of mucoadhesion was introduced in the field of controlled release drug delivery systems in the early 1980s. For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier

system to a specific biological location. If adhesive attachment is to a mucous, the phenomenon is referred to as mucoadhesion. Mucoadhesion is relatively new concept in drug delivery system. Mucoadhesion delivers the drug by adhering to the mucus membrane [1, 2].

Various mucosal routes for drug delivery are-

- Buccal /oral route
- Nasal route
- Ocular route
- Vaginal route
- Gastrointestinal route

The advantages of mucoadhesive drug delivery system:

- Prolongs the residence time of the dosage form at the site of absorption.

- Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug.
- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Increase in drug bioavailability due to first pass metabolism avoidance.
- Drug is protected from degradation in the acidic environment in the gastrointestinal tract.
- Improved patient compliance- ease of drug administration.
- Faster onset of action is achieved due to mucosal surface (pranshu Tangri) [3].

Mechanism of mucoadhesion: Mucoadhesion is the fixing of the drug to the mucous membrane by using a suitable carrier. It's a complex phenomenon which include wetting, adsorption and interpenetration of polymer chains. Following mechanism involve in mucoadhesion process such as [4].

- Wetting or swelling phenomenon (intimate contact of mucoadhesive to the mucous membrane).
- Interpenetration (Penetration of the bioadhesive into the mucous membrane)

Contact time for all most mucosal routes is hardly an hour, it can be improve by the addition of an adhesive polymer in the delivery system which is useful to localize the delivery system and increases the residence time at the absorption site. The right mechanism of mucoadhesion is still have to establish but an accepted theory explain that an intimate contact between the mucoadhesive polymer and mucin takes place which is followed by the interpenetration of polymer and mucin. Due to the formation of van der Waals forces, electrostatic bonds and hydrogen bonds increases the adhesion process [5, 6, 7].

The mucoadhesion mechanism is generally involves two steps

- Contact stage
- Consolidation step.

Contact stage: It is a stage at which contact of mucoadhesive polymer to the mucus membrane, by wetting, spreading and swelling of the delivery system.

Consolidation step: It involves the activation and bonding of Mucoadhesive agent. The mucoadhesive materials are activation is due to the presence of moisture. Moisture increase the plasticity of the system, allowing the mucoadhesive molecules to

break free and to link up by hydrogen bonds and weak Vander Waals force.

Theories of mucoadhesion: Bioadhesion occurs by a complex mechanism. . There are various terminological subsets of adhesion depends upon the environment in which the process occurs. Here following theories have been given which can help us to improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of Bioadhesion [8]. The theories are,

The wetting theory: The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Vander Waal's forces, for the adhesive interaction amongst the substrate surfaces. It is proposed that lower contact angle of liquid on the substrate will show higher affinity for the liquid to the substrate surface. In the presence of liquid If two substrate surfaces are brought in close contact with each other, the liquid cause's adhesion between two surfaces.

The mechanical theory: The mechanical theory states that the diffusion of the adhesive liquid into the micro-cracks and irregular micro-cavity on the substrate surface causes adhesion due to the formation of interlock structure

The diffusion theory: According to this theory, diffusion of the polymer chains, forms a network structure present on the substrate surfaces, across the adhesive interface

The adsorption theory: This theory shows that the presence of forces between the molecules, like, Vander Waal's forces and hydrogen bonding, are the main cause of adhesion amongst the substrate surfaces.

The electronic theory: The theory involves movement of ions (electron) amongst the surfaces resulting in the development of an electrical double layer which gives rise to attractive forces.

The cohesive theory: according to this theory that the bioadhesion are mainly due to the intermolecular interactions between like-molecules [9, 10]. On the basis of above theories, the bioadhesion process can be classified into two categories, Chemical method (electronic and adsorption theories) Physical method (wetting, diffusion and cohesive theory) [11, 12].

The process of adhesion may be divided into two stages- During the first or contact stage, wetting of mucoadhesive polymer and mucous membrane was

occurs and followed by the consolidation stage, where the physicochemical interactions take place [13]. The term “mucoadhesion” was defined as the adhesion of the polymers with the surface of the mucosal layer. The main components constituting the mucosa include water and mucin (an anionic polyelectrolyte), while the other components include proteins, lipids and mucopolysaccharides. Water and mucin constitute > 99% of the total composition of the mucus and out of this > 95% is water. The gel-like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoprotein along with the non-covalent interactions (e.g. hydrogen, electrostatic and hydrophobic bonds) which results in the formation of a hydrated gel-like structure and explains the visco elastic nature of the mucus [14].

Polymers Used For Mucoadhesive Drug Delivery

Mucoadhesive drug delivery systems are being discovered for the localization of the active component to a specific site. In the designing of such dosage form polymers played a very important role that's increase the residence time of the active component at the target site. Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable network, joined by cross linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

An ideal polymer for a bio adhesive drug delivery system should have the following characters is as follows [15].

- Polymer and its degradation products should not be toxic, irritant & absorbable.
- It should preferably form a strong non covalent bond with the mucus cell.
- It should possess some location specificity and stick quickly to moist tissue.
- It should provide easy incorporation of the medicament and do not interfere with its release pattern.
- Polymer must have a good stability and do not degrade during the shelf life of the dosage form.
- Its cost should be cheap so that prepared dosage form remains competitive.
- For a good mucoadhesive property Polymer should have high molecular weight up to 100.00 [16].
- For the interpenetration long chain polymers-chain length must be long enough

to promote it, and should not be too long that cause diffusion and it is problematic.

- Viscosity should be high.
- Chain mobility and resistance to dissolution affect by or influence by degree of cross linking. Those polymers which is highly cross linked swell in water and maintain their structure. Swelling favors sustained release of the drug and increases interpenetration. The mucoadhesive strength is reduces by reducing the chain mobility which is caused by over/high cross linking [17].
- Polymer chain flexibility shows good interpenetration of the polymer into the mucus network.
- Polymer concentration- an optimum polymer concentration is necessary for a proper mucoadhesion. However, it depends on the dosage form. In case of solid dosage form the mucoadhesive property increases with increase in the concentration of polymer. But in semi-solid dosage forms beyond an optimum concentration the adhesive strength decreases [18, 19].
- Charge and degree of ionization- Bernkop-Schnurch and Freudl shows the effect of polymer charge on the adhesion. In this work, different chemical entities was attached to chitosan and the mucoadhesive strength were measured. Chitosan HCL showed marked mucoadhesiveness when compared to the control which is cationic in nature. The attachment of an anionic group e.g. EDTA enhanced the mucoadhesive strength significantly. Cationic chitosan and anionic EDTA chitosan complexes exhibit more mucoadhesive strength than DTPA/chitosan system because of high charge. Hence the mucoadhesive property can be given as anionic < cation < anion.
- Optimum hydration- over hydration decreases mucoadhesive strength due to formation of a slippery mucilage [20, 21].
- Optimum pH – mucoadhesive property is optimum at low pH value but at higher pH condition a change in the conformation occurs into a rod like structure and cause inter diffusion and interpenetration [22]. At very high pH condition, cationic polymers like chitosan form complexes of polyelectrolyte with mucus and gives strong mucoadhesive forces [23].

Advantages:

- Biodegradable and nontoxic and non-irritant

- Good tableting formulation flow ability.
- Are safe and effective for oral administration
- Are bioadhesive and providing increased bioavailability
- Long drug release profiles can give drug releases profiles similar to carbopol 9710NF,
- Have better handling characteristics
- Are approved by many pF the world pharmacopoeias
- Protect protein and peptides from degradation and hence increase the bioavailability of proteins or peptide based formulations.

Classification

Cationic Polyelectrolytes: cationic polymers exhibit good biocompatibility and biodegradable properties due to that it's used in designing of mucoadhesive dosage forms. E.g. Chitosan, its cause mucoadhesion by reacting with negatively charges mucin.

Anionic polyelectrolytes: Anionic polyelectrolytes exhibit strong hydrogen bonding with the mucin of the mucosal layer that's why most preferably used in designing of mucoadhesive drug delivery system. E.g. carboxy methyl cellulose and (PAA) poly acrylic acid.

Non-Ionic Polymers: Non-ionic polymers shows mucoadhesive properties. It's hydrophilic and form viscous solutions with water due to that it can be used as viscosity modifying agents in the formulation of various delivery systems to enhance the bioavailability of the drug. E.g. HPMC, poloxamer, MCC, poly vinyl pyrrolidone (PVP) and poly vinyl alcohol (PVA).

Hydrophilic polymers: These polymers soluble in water & swell when come in contact with aqueous media with dissolution of the matrix. The polyelectrolyte's have better mucoadhesive property compared with neutral polymers.

Hydrogels: It is three-dimensionally cross linked polymer chains exhibits ability to retain water within its porous structure. This property of the hydrogels is mainly due to the presence of hydrophilic functional groups like, amino, hydroxyl and carboxyl groups. Poly acrylic acid and sucrose are used to prepare hydrogel by using condensation reaction.

Lectin-based polymers: these are proteins found in animal and plant kingdom which have ability to attach reversibly with specific sugar carbohydrate residues. The specific cyto-adhesive property of lectins to the carbohydrate residues gives them with special property and is being used to design targeted drug delivery systems. Legumes are the source of

lectins from which it is extracted and used to explore and develop targeted drug delivery system. Lectins are natural proteins that are useful in the recognition of proteins and cells.

Thiolated polymers: in the polymeric chain presence of free thiol group helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can strongly improve the mucoadhesiveness of the polymers e.g. chitosan thioglycolic acid, poly (acrylic acid)-homocysteine, poly (acrylic acid)-cysteine, chitosan-aminothioline, chitosan-thioethylamine, sodium carboxy methyl cellulose-cysteine, poly (methacrylic acid)-cysteine and alginate-cysteine. The presence of the thiol group increases the contact time by promoting covalent bonds with the cysteine in mucus. The disulphide bonds also affect the drug release mechanism from the dosage form due to increased cross linking and rigidity. Ex. Paacystiene, chitosan iminothiolane PAA homocystiene, Alginate cysteine

Characteristics of an ideal mucoadhesive polymer:

- The polymer should be nontoxic. It degrades in stomach and form degradation product should be nontoxic and not absorbable in gastrointestinal tract (GIT).
- It should be inert and not causing any irritation to the mucus membrane.
- It has a capability to adhere quickly on the surface of tissue and should possess some site-specificity.
- It should be able to form a strong non-covalent bond with mucin on the surface of epithelial cell.
- The polymer should not be decompose on storage or during the shelf life of the dosage form.
- The cost of polymer should be cheap therefore the preparation of dosage form can be easily performed [24].

Robinson and his group, using the fluorescence technique, concluded that

- The anionic and cationic polymers adhere to the mucus membrane more effectively than neutral polymers.
- Anionic polymers attach to the sulfate groups bind more effectively to the surface of mucus membrane other than carboxylic groups attach with the anionic polymers.
- The water insoluble polymers have greater flexibility to form dosage form as compared to water soluble polymer. Polyanions

showing greater binding properties as compare to polycations.

- On the polymer the charge density is proportional to the degree of binding
- The polymer which is having highly binding strength includes gelatin, carbopol, polycarbophil, carboxymethyl cellulose and hyaluronic acid [25].

Molecular characteristics:

Many authors investigate the various molecular characteristics in polymers and determine the conclusion with the regarding of molecular characteristics which is required for mucoadhesion. The molecular characteristics required for mucoadhesion in polymer may be such as following.

- The mucoadhesive polymer should have Strong hydrogen bonding groups (-OH, -COOH).
- Having Strong anionic charges.
- Sufficient flexibility to penetrate the mucus network or tissue crevices.
- The polymer should have Surface tension characteristics to achieve wetting of mucus or mucosal tissue surface.
- The drug which have greater molecular weight responsible for good mucoadhesion. Although the anionic nature of the polymer is preferable for a good mucoadhesive, a cationic for example chitosan and nonionic molecule such as cellulose derivative can be used successfully [26, 27].

Natural Mucoadhesive Polymers

Chitosan:

Chitosan is a natural polymer derivative of chitin. Commercial chitosan is derived from the shells of shrimp and other sea crustaceans, including *Pandalus borealis*. It is a linear polysaccharide composed of randomly distributed β -(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit).

Properties

- Mucoadhesive nature
- Used in trans-dermal drug delivery.
- In drug delivery, it shows positive charge under acidic conditions.
- It is insoluble in neutral and basic environments.
- Chitosan may form many translational metal ions.
- Ability of specific cellular action for target drugs.
- It has bacteriostatic and fungi static effect.

- Ability to attach itself to other molecules.

Advantage of chitosan: Chitosan have good biocompatibility and low toxicity that makes it a good pharmaceutical excipient in both conventional and novel applications [28].

Pectins: It is made up of mixture of polysaccharides. Citrus peel or apple pomades are the main source of pectin, both of which are by-products of juice manufacturing process Apple pomade contains 10–15% of pectin on a dry matter basis while Citrus peel contains of 20–30%. Pectin is mainly composed of D-galacturonic acid units joined in chains by means of α -(1-4) glycosidic linkage. These uronic acids have carboxyl groups, some of which are naturally present as methyl esters and others which are commercially treated with ammonia to produce carboxamide groups. Pectins are soluble in pure water. Mono alkali metal of pectic acids are soluble in water; di- and tri-valent cations salts are weakly soluble or insoluble. Dry powdered pectin, forms clumps when added to water. Pectin has been used in the pharmaceutical industry for a wide range of.

Pharmaceutical applications

- Used as binding agent in tablets.
- High methoxy pectin used as monolithic bioerodable system.
- Use in the preparation of directly compressed tablet along with HPMC.
- Low methoxy pectin used to prepare beads by inotropic gelation method.
- Also used in the sustained release drug delivery system.

Tragacanth: It is a natural gum obtained from the dried juice of various species of the genus *Astragalus*, including *A. gummifer*, *A. ascenders*, *A. tragacanthus* and *A. brachycalyx*. Tragacanth gum is an odorless, tasteless, viscous and water-soluble mixture of polysaccharides.

Pharmaceutical applications

- It is used as adhesive agent for tablets and pills.
- Used as thickening agent
- Tragacanth used as emulsifying oil droplets in creams, paste and lotions.

Sodium alginate: Alginic acid is an anionic polysaccharide, also known as algin and found in the cell walls of brown algae. It has ability to bind with water and form a viscous gum. Alginic acid is having property to absorb 200-300 times of its own weight in water when water extracted from alginate. It is mainly extracted from seaweed. Generally alginic acid is

produced by two bacterial genera such as Azotobacter and Pseudomonas. These bacteria play a vital role in the preparation of its biosynthesis pathway. The salt of alginic acid is called sodium alginate. Its molecular formula is $\text{NaC}_6\text{H}_7\text{O}_6$. Sodium alginate is a gum which extracted from the cell walls of brown algae. Sodium alginate is soluble in water and insoluble in ethanol and ether.

Pharmaceutical applications

- Sodium alginate is odorless gum, used as viscosity modifying agent in the food industry.
- It is used as emulsifying agent
- Used in indigestion tablets and the preparation of dental impressions.
- It acts as a chelating agent and used to pull radioactive toxins from the body.
- It is also used in immobilizing enzymes by inclusion.

Guar gum: It is naturally occurring form of galactomannan, also known as guaran. It is mainly obtained from endosperm of guar beans. It constitutes about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. Its molecular weight is too high, approximately 1 million. The high viscosity of guar gum is due to its long chain structure and high molecular weight. Guar gum is a polysaccharide composed of the sugars galactose and mannose. Guar gum is soluble in cold and hot water but insoluble in many organic solvent

Pharmaceutical Application:

- Guar gum used as binder or as disintegrants in tablets.
- It is used in some bulk-forming laxatives.
- In cosmetics and toiletries industries.
- Used as thickener in toothpastes and conditioner in shampoos.
- Emulsifying, stabilizing and film forming agent.
- Also used in targeting of colon due to release retarding property.

Isapgulla husk (Psyllium): Psyllium seed husks, also known as ispaghula, isabgol, or simply as psyllium, are portions of the seeds of the plant *Plantago ovata*. Gel forming fraction of the alkali-extractable polysaccharides is composed of arabinose, xylose and traces of other sugars.

Properties: They are water soluble, swell and becoming mucilaginous in the presence of water. It is

white fibrous material, hydrophilic in nature and forms a clear colorless mucilaginous gel by absorbing water.

Pharmaceutical Applications:

- Used as binder and disintegrants in different tablet dosage form.
- Also used as release retarding agent to control the drug release.
- In the production of commercial mucilage.
- Also used in targeting the colon due to release retarding ability [29].

Gelatin: Gelatin is a mixture of peptides and proteins produced by partial hydrolysis of collagen extracted from the boiled bones, connective tissues, organs and some intestines of animals. There are two types of gelatin. Soft gelatin obtained by acid hydrolysis Hard gelatin obtained by alkali hydrolysis. It is an irreversible hydrolyzed form of collagen, formed by breaking apart its natural triple-helix structure into single strand molecules. It is non-immunogenic compared to collagen;

Pharmaceutical Applications

- Used in wide range of food and nonfood products.
- Used as stabilizer and thickener.
- Used in the preparation of soft and hard gelatin capsules.
- Also acts as an adhesive agent
- Also used in the masking of taste.

Synthetic Polymer:

Carbopol: It is a polymer of acrylic acid crosslink with divinyl glycol or polyalkenyl ether. It form a gel when expose to a PH of 4-6. they can swell in water up to 1000 times.

Pharmaceutical application:

- It have good flow properties therefore it is used Good tableting formulation.
- It have greater mucoadhesive strength therefore prolong the drug release.
- It can give drug releases as similar to carbopol 971 NF, with better handling characteristics.
- It is mucoadhesive in nature and providing increased bioavailability.
- It is nontoxic and safe and good effective for oral administration.
- It protect form the protein and peptides degradation and increase the bioavailability of proteins or peptide based formulations [30].

Semi-Synthetic Mucoadhesive Polymers**Sodium Carboxy Methyl Cellulose (sod.CMC):**

Sod. CMC is a water-soluble polymers they swell instantly when comes in contact with water and subsequently undergo complete dissolution.

Pharmaceutical Applications

- Used as emulsifying agent in pharmaceuticals and cosmetics.
- Also used as thickening, binding and stabilizing agent.
- It is also used in the preparation of microspheres by crosslinking with gluteraldehyde [31].

Hydroxy propyl cellulose (HPC)

It is non-ionic water-soluble and pH insensitive cellulose ether.

Pharmaceutical Applications

- Used as thickening agent.
- As a binder in tablets.
- Also used as a release retarding agent
- Used in film coating.
- Also used in mucoadhesive drug delivery system for various drugs.

HPMC: It is a water soluble cellulose ether, forms a viscous solution with water. Mainly used in the formulation of controlled release tablets. Viscosity is the main factor which is responsible for controlling the release. Ifat Katzhendler *et al.* studied the effect of molecular weight of HPMC on the mechanism of drug release of naproxen sodium (NS) and naproxen (N) [168]. The prolong drug release of the active ingredient is due to the hydration and gelling abilities of HPMC.

Hydrogels Polyvinyl pyrrolidone (PVP): PVP is a water soluble polymer. Molecular weight ranging from 40,000 -360,000. It is synthesized by polymerization of vinylpyrrolidone in water or isopropanol. PVP is available in different grades based on molecular weights. It is mainly used as a binder in tablet formulations. When compared to other binders, wet granulation with PVP having a

molecular weight of 25,000 to 90,000 generally gives harder granulates with good flowability, higher binding and low friability. In addition to enhancing the above properties, PVP also improve the dissolution of the active ingredient. Formulation of paracetamol (Acetaminophen) tablets with 4% PVP 90,000 as binder, gives the quickly release of the drug than tablets with gelatin or hydroxypropyl cellulose as binder. A lots of the active ingredients shows poor aqueous solubility due to that they have limited bioavailability. Bioavailability of an active substance can be easily enhance by improving its dissolution by incorporating asolubilizing agent, e.g. soluble PVP grades. These form water-soluble complexes with many active substances and enhance bioavailability. The bioavailability of per oral gidazepam was enhanced by the addition of povidone. Soluble grades of PVP and polyvinyl pyrrolidone-vinyl acetate (PVP-VA) copolymer have been used to enhance the bioavailability of various poorly water soluble drugs. E.g. tolbutamide, nifedipine, indomethacin.

CONCLUSION

Mucoadhesive polymers are used in mucoadhesive drug delivery system because it improves the residence time of active entity at the delivery site. Mucoadhesive polymers can be used to improve the drug delivery through the various different routes such as nasal, buccal, oral, gastrointestinal, ocular as well as vaginal and rectal. Advantages of Polymers used are mucoadhesion, an increase in the residence time of the polymer, penetration enhancement, and enzymatic inhibition. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future. This class of polymers has enormous potential for the delivery of therapeutic macromolecules, genes, and vaccines. Mucoadhesive dosage forms have a high potential of being useful means of delivering drugs to the body.

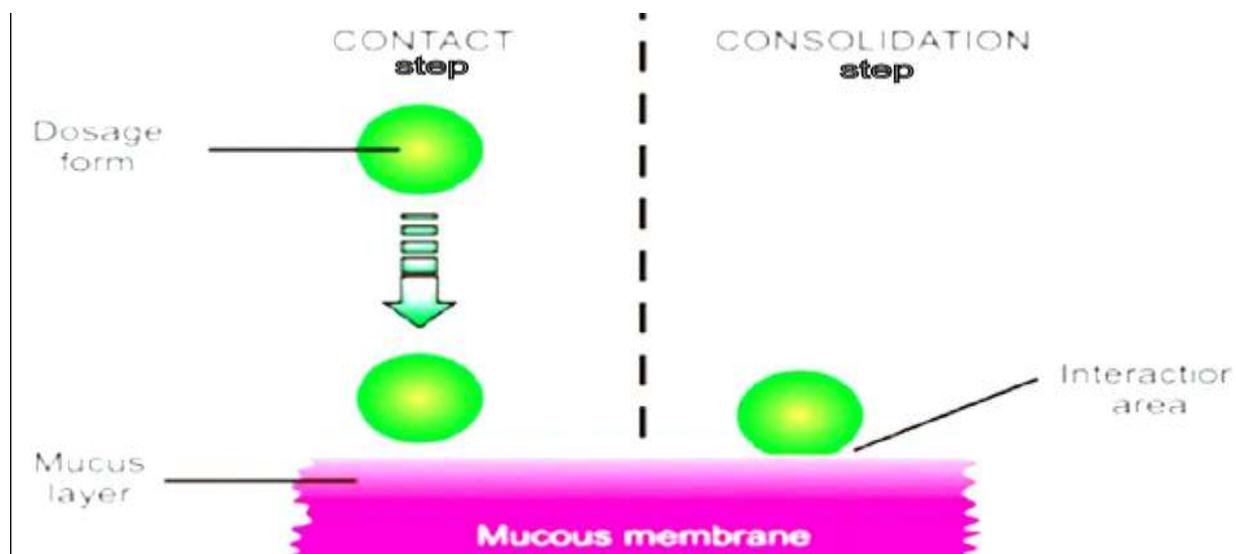


Fig. Mechanism of mucoadhesion

Table1: Mucoadhesive Polymers with nature and their Bioadhesive Property

S.No	Polymer	Bio-adhesive Property	Types of Polymer
1.	CMC Sodium	+++	Semi-synthetic
2.	Carbopol 934	+++	Synthetic
3.	Polycarbophil	+++	Synthetic
4.	Tragacanth	+++	Natural
5.	Chitosan	+	Natural
6.	Sodium Alginate	+++	Natural
7.	Hydroxy Ethyl Cellulose	+++	Semi-synthetic
8.	HPMC	+++	Semi-synthetic
9.	Gum Karaya	++	Natural
10.	Gelatin	++	Natural
11.	Guar Gum	+	Hydrophilic
12.	Thermally Modified Starch	+	Natural
13.	Pectin	+	Hydrophilic
14.	PVP	+	Hydrogel
15.	Acacia	+	Natural
16.	Psyllium	+	Natural
17.	Hydroxy Propyl Cellulose	+	Semi-synthetic

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