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A SYSTEMATIC REVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The prospect of writing this review article is to present comprehensive information related to mucoadhesion and mucoadhesive drug delivery systems. The article has highlighted all the aspects of mucoadhesive drug delivery systems which will be helpful for researches and academics. The article includes detailed information about mucosa- the anatomy and physiology, the mechanisms and theories related to mucoadhesion, evaluation parameters of mucoadhesive dosage forms, mucoadhesive polymers and novel approaches related to mucoadhesive drug delivery system. The potential merits and demerits of mucoadhesive drug delivery as well as that of the polymers are also discussed.

KEYWORDS: bioadhesion, factors, mucosa, mucoadhesion, parameters, polymers.

INTRODUCTION

In the recent years, mucoadhesion drug delivery system has shown remarkable interest for increasing the residence time at the site where it is applied and to expedite intimate contact of the dosage form with the underlying mucosa, mainly to promote absorption and elevate the percentage bioavailability of drug due to its extensive surface area and high flow rate of blood.[1] Mucosal drug delivery bypasses the hepatic first-pass thus avoids the degradation decadence by enzymes present in gastrointestinal tract. Thus this system could be assessed in delivering an enlarging number of high molecular weight molecules like proteins and peptides. Mucoadhesive controlled drug delivery systems are valuable, since they not only give a controlled but also targeted release and thus site specific delivery. Mucoadhesive

substances are not only used for systemic effects but are also explored for local therapeutic actions like to coat, protect and soothe the injured tissues (stomach ulcers or lesions in the oral mucosa) or as lubricants (in the oral cavity, eye and vagina).[2]

Bioadhesion and Mucoadhesion

'Bioadhesion' widely encompasses adhesive interactions with any biological or biologically derived substance.[3,4] For the drug delivery, bioadhesion is utilized to construe the adhesion between synthetic or natural polymers and mucosal soft tissues.[5,6] 'Mucoadhesion' can be used when the bond with a mucosal surface is formed. Mucoadhesion may be defined as a state in which two components, one from the biological source, are joined together for prolonged periods of time by the aid of interfacial forces.[7] Bioadhesion can be classified into 3 types:

• adhesion between two different biological phases.

• adhesion of a biological phase to an artificial substrate.

• adhesion of an artificial material to a biological substrate.[8-10]

Mucous Membrane

Mucous membrane as shown in Fig. 1[98] is the main site of administration for bioadhesive systems. A mucosa consists of two to three layers: (1) an epithelium, (2) lamina propria, (3) a layer of smooth muscle called the muscularis. They are characterized by a layer of epithelium, whose surface is covered by mucus.[3,11] Mucin, a glycoprotein of mucus, is responsible for the structure of mucus membrane. Thickness of mucus can vary from 50-500 μm in the stomach to less than 1 μm in the mouth cavity.[12-13]

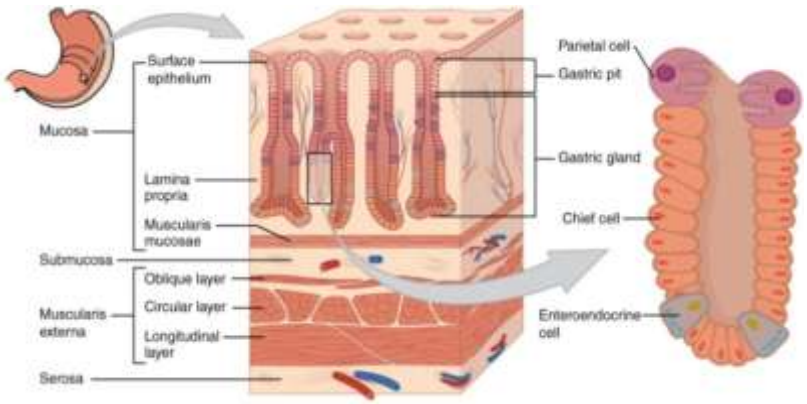

Fig. 1: Composition of mucous membrane.[98]

Composition of mucus layer

The mucus consists of glycoproteins, fats, salts and about 95% of water by mass, making it a highly hydrophilic system.[3,12] Mucus glycoproteins are high molecular weight proteins possessing attached oligosaccharide units containing, L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and Sialic acid.[14,15]

Functions of mucus layer

Mucous membranes have absorptive, secretory, and protective functions. Mucous layer is protective because of its hydrophobicity.[3]

- It influences the bioavailability of drugs as it hinders the tissue absorption of drugs and other substrates.[12]
- It strongly bonds with the epithelial cell surface as a continuous gel layer i.e. helps in adhesion.
- It has key part in the lubrication of the mucosal membrane and maintenance of its moisture.[14]
- They are often covered with mucus secreted by goblet cells, multicellular mucous glands, or both. The mucus traps bacteria and foreign particles, which keeps them from invading the tissues and aids in their removal from the body.[15]

ROUTES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

Mucoadhesive drug delivery system includes:

1. Buccal and sublingual delivery system;
2. Nasal delivery system;
3. Ocular delivery system;
4. Vaginal and rectal delivery system;
5. Gastrointestinal delivery system.

1. Buccal and sublingual delivery system

The buccal cavity has a surface area of about 45 cm^2 but the accessibility of the site makes it preferable for delivering therapeutic moieties.[12] Delivery through this site avoids hepatic first-pass metabolism and also aids in local remedy of the oral infections. The buccal cavity offers low enzymatic activity.[16-18] Moreover; it can be instantly discontinued in cases of toxicity by removing the dosage form.[20] The sublingual mucosa is comparatively more permeable than the buccal mucosa; hence used for immediate release formulations.[19]

2. Nasal drug delivery system

The nasal mucosa has a surface area of about 150-200 cm^2 but the residence time in the nasal mucosa is between 10 to 30 min.[17] This short time is due to the surged activity of the mucociliary layer triggered by foreign particles.[4] Nasal cavity avoids first-pass as it has highly vascularized surface area and blood conduits directly from the nose into the systemic circulation. The utmost use here is of intranasal active ingredients in solution form which contain sympathomimetic vasoconstrictors for prompt relief from nasal congestion.[12,18]

3. Ophthalmic drug delivery systems

There is a prompt removal of active pharmaceutical ingredient from the ocular cavity due to myriad reasons like constant tear formation, blinking of eyes as well as lacrimal drainage which results in the reduced bioavailability of the active ingredients and this can be declined by delivering the medicaments using ocular inserts or patches.[12,21] Also, the holding capacity of eye is only about 30µl. This problem can be solved by using various types of dosage forms including liquid drops, gels, ointments and solid ocular inserts to improve retention time. Another interesting delivery system is in situ gelling polymer that experience a phase transition due to ionic change, pH change or temperature change after application. Mucoadhesive polymers would only adhere to conjunctival mucus membrane *in vivo.*[17,18]

4. Vaginal and rectal drug delivery

Vaginal and rectal routes have been explored for the delivery of the active agents both locally and systemically.[4] These routes have some advantages due to its enormous surface area, heavy blood supply, relatively high permeability to many drugs and self-insertion.[12,23] Also it avoids hepatic first-pass, resulting in decreased hepatic side effects and avoids pain, tissue damage, and infection.[17] Furthermore, residence time in the vagina is much higher than at other absorption sites such as the mucosa of rectum or intestine.[18]

5. Gastrointestinal drug delivery

Gastrointestinal mucosa is also an important site for the development of mucoadhesive dosage forms for increasing GI transit time as well as bioavailability.[2] The probable occurrence of local ulcers as a side effect due to the intimate contact of the dosage form with GIT mucosa for extended periods of time should not be neglected.[12] The mucus turnover, that is, the unceasing production of mucous by the gastric mucosa to replace the lost mucous through peristaltic contractions and the dilution of the stomach content also limits the possibilities of mucoadhesion as a gastro retentive force.[5,11]

MECHANISM OF MUCOADHESION

The mucoadhesive dosage form must proliferate over the substrate to induct a close contact and hike the surface contact, assisting the diffusion of mucus chains.[31,32] Attraction and repulsion forces arise and the attraction forces must dominate for a mucoadhesion to be successful. The first two steps i.e. contact stage and consolidation stages are shown in Fig. 2.[24]

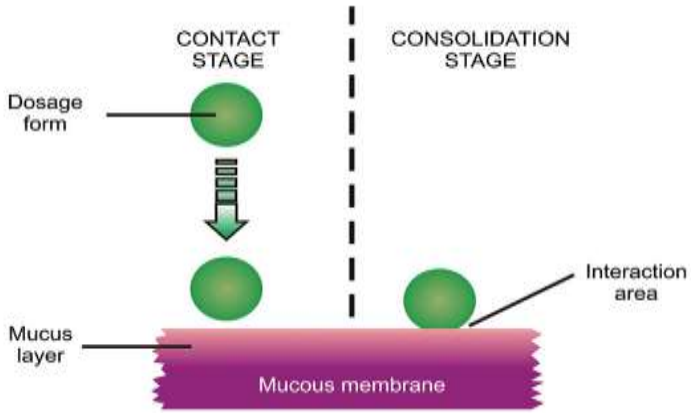

Fig. 2: **The two steps of the mucoadhesion process.[24] [with permission].**

Step 1: Contact Stage

The wetting and subsequent swelling step ensues when the polymer spreads over the mucosal membrane in order to establish an intimate contact with the substrate. Polymer swells because the polymer components have an affinity for water.[24,30] In ocular, buccal or vaginal formulations, the delivery system is mechanically bound to the membrane. In other cases, the deposition is due to the aerodynamics of the organ to which the formulation is administered, like for the nasal route.[27,28] While in the gastrointestinal tract, peristaltic motions can contribute to this contact. If the particle advances to the mucous surface, it comes into contact with repulsive and attractive forces. Thus, the particles must overcome the repulsive barrier for contact to ensue.[3]

Step 2: Interpenetration Stage

The mucous membrane surface has high molecular weight polymers called glycoproteins**.** In step 2 of the bioadhesive bond formation, the mucosal polymer chains and the bioadhesive polymer chains intermingle and embrangle to form adhesive bonds.[3] The bond strength depends on the degree of inter-penetration between the two polymer groups. If both the polymers are of similar chemical structure i.e. both are hydrophilic, then strong chemical bond is formed.[5,34]

Step 3: Consolidation Stage

In the consolidation step, activation of mucoadhesive materials occur in presence of moisture where the mucoadhesive molecules break free and link up again by weak Van der Waals and hydrogen bonds. Basically, two theories explain the consolidation step: the theory of diffusion and the theory of dehydration.[12,24] According to the theory of diffusion, the mucoadhesive materials and the glycoproteins of the mucus collectively interact through entanglement of their chains and forming of secondary bonds.[26,33] According to the theory of dehydration, as shown in Fig. 3,[24] materials that easily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the osmotic pressure difference. Water is drawn into the formulation due to concentration gradient until the osmotic balance is reached leading to rise in contact time.[25,29]

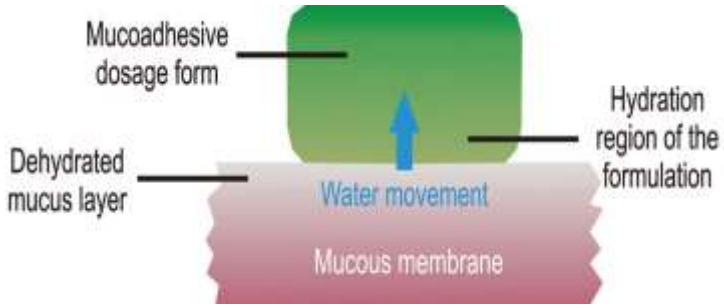

Fig. 3: Dehydration theory of mucoadhesion.[24] [with permission]

ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS[3,35-39]

- Increases the residence time of formulation at the site of absorption, hence surges the bioavailability.
- Excellent accessibility, rapid onset of action possible.
- Quick absorption because of tremendous blood supply and good perfusion rates.
- Better patient compliance.
- Rapid healing and cellular recovery of the local site.
- Lower dosing frequency.
- Short treatment period.
- Increased margin of safety for highly potent drugs due to improved control of plasma level concentration.
- Maximum utilization of drug enabling reduction in total quantity of drug administered.

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS[3,35-39]

- Drugs irritatinge the oral mucosa, having an unpleasant taste, odor or unstable at buccal pH cannot be administered by this route. Eating and drinking may hinder the dosage form or it may be restricted.
- Medicaments with less dose requirements can only be administered.
- Drugs may be swallowed along with the saliva and lose the advantages of buccal route.
- Drugs whose absorption is by passive diffusion can only be administered by this route.
- In case of vaginal drug delivery, the drug has to be stable in the acidic vaginal pH. The vaginal formulation may leak and cause messiness. The vaginal formulation may be contraindicated in case of pregnancy.
- In case of ocular formulations, the formulation may cause uneasiness and blurring.
- The dosage form given by any route may get dislodged from its position.
- In case of nasal formulations, the presence of the formulation may stimulate sneezing and subsequent dislodgement of the formulation. The formulation may irritate the sensitive nasal mucosa.
- Over hydration may structurally disrupt the formulation or forms slippery surface due to swelling and hydration of the bioadhesive polymers.

Theories of Mucoadhesion / Bonding Mechanism

There are six traditional theories which have resulted from studies on the performance of variety of materials and polymer- polymer adherence. The classification of these theories is shown in Fig. 4. The contact angle and time of contact plays a significant role in mucoadhesion as shown in Fig. 5.

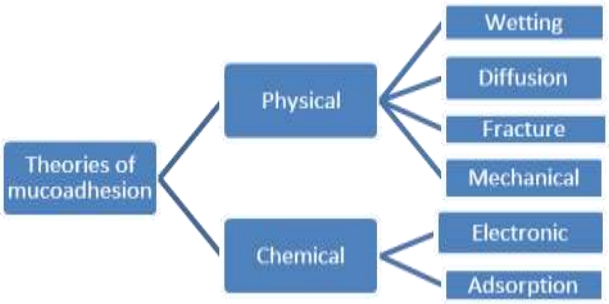

Fig. 4: Classification of theories of Mucoadhesion.

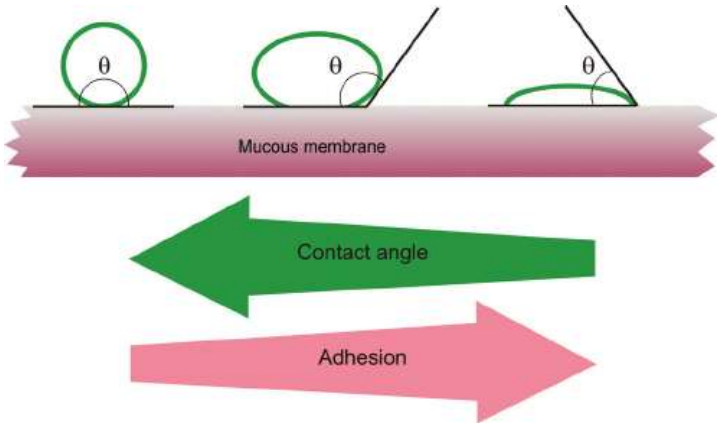

Fig. 5: Influence of Contact angle between device and mucous membrane on bioadhesion.[24] [with permission]

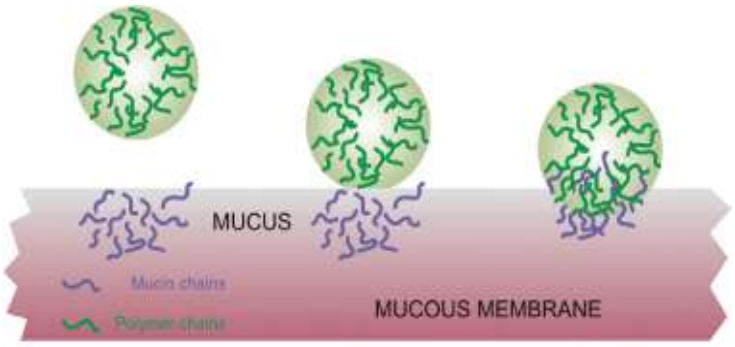

Fig. 6: The secondary interactions resulting from inter-diffusion of polymer chains of bioadhesive device and of mucus.[24] [with permission]

Wetting theory

The affinity between the liquid systems and the mucus membrane is obtained by ascertaining the contact angle.[15] As a basic concept, as the contact angle decreases, the affinity increases. The contact angle must be near to zero to provide sufficient spreadability.[42] Fig. 6 is an illustrative diagram showing effect of contact angle between the dosage form and mucous membrane.

The spreadability coefficient, S_{AB}, is measured from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB}, as indicated in equation:

$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$

Higher the individual surface energy of mucus and device in relation to the interfacial energy, more is the work of adhesion, WA.

$WA = \gamma_A + \gamma_B - \gamma_{AB}$[40,41,43]

Diffusion theory

The diffusion theory explains the phenomenon of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains. As the bond strength enhances, the degree of the penetration increases.[24,25] The secondary interactions due to inter-diffusion can be seen in Fig. 6. Diffusion coefficient, polymer chain flexibility, nature of mucoadhesive chains, mobility and contact time of polymer chains are the factors on which the degree of penetration depends. The depth of interpenetration required to produce a firm bio adhesive bond lies in the range 0.2–0.5 μm.[3] This depth of interpenetration of polymer and mucin chains can be found out by the following equation:

The interpenetration depth, $I= (tDb)^{1/2}$

Where t = contact time and Db = diffusion coefficient of the mucoadhesive material in the mucus.

For diffusion to ensue, it is crucial that the systems involved have good mutual solubility, that is, both the bio adhesive and the mucus should have identical chemical structures.[40,41]

Fracture theory

This theory examines the force needed to dissociate two surfaces after adhesion is established.[24,26] The work of fracture has been found to rise when the polymer network fibres are longer or if the degree of cross-linking within such a system is decreased.[15,25] This concept aids in the measurement of fracture strength (σ) after the separation of two surfaces via its relationship to the Young's modulus of elasticity (E), the fracture energy (ε) and the critical crack length (L) through the following equation: $\sigma=(E*\varepsilon/L)^{1/2}$

The force, S_m, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m, and the total surface area, A_0, involved in the adhesive interaction:

$S_m= F_m/A_o$[42]

The regions of mucoadhesive bond rupture can be seen in Fig. 7.

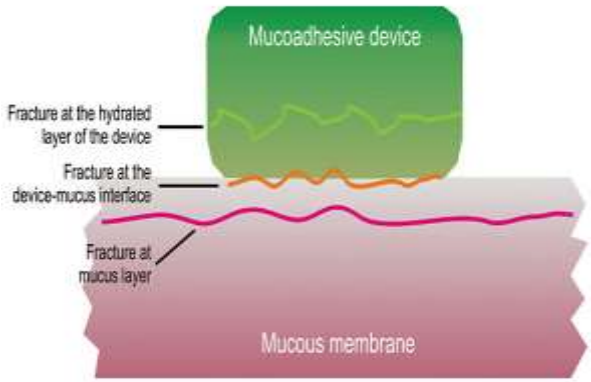

Fig. 7: Regions of mucoadhesive bond rupture can occur.[24] [with permission]

Mechanical theory

Mechanical theory proposes that the adhesion is because of the filling of the imperfections of a rough surface by a mucoadhesive liquid.[3,40] The irregularities enhances the interfacial area available for interactions thus enhancing energy dissipation. The mechanisms ruling mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied.[24-26] Intrinsic factors of the polymer are related to its molecular weight, concentration and chain flexibility. For linear polymers, mucoadhesion is directly proportional to molecular weight, but the same does not hold for non-linear polymers.[44]

Electronic theory

The electronic theory relies on the hypothesis that the bioadhesive material and the target mucous membrane have diverse attributes of electronic surface.[3,40] Based on this, when the surfaces come in contact with each other, there is an electron transfer to balance the Fermi levels, arising due to the formation of electrical double layer at the interface of the bioadhesive and the mucous membrane. The bioadhesive force is assumed to be present due to the attractive forces over this double layer.[26,44]

Adsorption theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak Van der Waals forces and hydrogen bond formation. Various mucoadhesive interactions are: Ionic bonding, Covalent bonding, Hydrogen bonding, Van der Waals bonding, Hydrophobic bonding.[15,24] For example, hydrogen bonds are the dominant interfacial forces in polymers having carboxyl groups.[41] These forces are very important in

the adhesive interaction phenomena because they might be individually weak, a great number of interactions can result in a strong global adhesion.[25]

Factors Affecting Mucoadhesive Drug Delivery Systems

A) Polymer related factors

1) Molecular weight- For a linear polymer, the bio adhesive property is directly proportional to the molecular weight. But in case of nonlinear polymer, the bio adhesiveness may or may not depend on molecular weight. The minimum molecular weight required for successful bio adhesion is at least 100,000.[4]

2) Concentration of active polymer- Optimum concentration of active polymer is required. In remarkably concentrated system, beyond a certain optimum level, the adhesive strength declines drastically because the coiled molecules become separated from the medium so the length of chain available for permeation become limited. When the concentration of polymer is very less, the number of penetrating polymer chains per unit volume of the mucous is small and the interaction between polymers and mucous becomes erratic.[26]

3) Flexibility of polymer chain- As water soluble polymer becomes cross linked, the individual polymer chain mobility drops and thus the effective chain length that can penetrate into the mucus layer reduces which decreases the mucoadhesive strength. Flexibility depends on the viscosity and diffusion coefficient. Higher polymer flexibility causes greater diffusion into mucus network.[25]

4) Spatial conformation– Despite having high molecular weight of about 2,00,00,000, the adhesive strength of dextrans is similar to that of PEG whose molecular weight is 100 times lesser. The helical, in contrast to linear conformation of polymers, may hide many active groups, which are responsible for adhesion, thus decreasing the mucoadhesive strength of the polymer.[25,46]

5) Swelling- Mucoadhesive polymer requires hydration to expand and form a proper macromolecular mesh of desired size and also to induce mobility in the polymer chain so as to increase theentanglement process between polymer and mucin. Swelling depends on the polymer concentration, ionic strength and the presence of water. The process of bioadhesion is dynamic and maximum *in vitro* bioadhesion occurs with optimum water content.[45]

6) Cross linking density– The average pore size, the average number molecular weight of cross linked polymers and the density of cross linking are three important and inter-related structural parameters of a polymer network. Higher the cross linking density, smaller is the pore size so that diffusion of water into the polymer network occurs at a slower rate, thus there is an insufficient swelling of polymer resulting in reduced penetration of polymer into the mucin.[40,26]

7) Hydrogen bonding capacity- The polymers should have functional groups like carboxylic and hydroxyl groups which can form hydrogen bonds. Polyvinyl alcohol, hydroxylated methacrylate and poly methacrylic acid and all their co-polymers are polymers with good hydrogen bonding capacity.[45]

8) Charge- The bioadhesive property of ionic polymer is always higher than that of non-ionic polymer. In neutral or slightly alkaline medium, the cationic polymer like chitosan depicts better mucoadhesive property.[25,26]

B) Environmental related

1) pH of polymer substrate interface- pH has an effect on the surface charge of both mucus and polymers. The charge density of mucus will differ depending on pH, because of variation in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which might influence adhesion.[27,41]

2) Applied strength- The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. Polymers become mucoadhesive even though they do not have attractive interactions with mucin if high pressure is applied for the sufficiently long period of time.[42]

3) Initial contact time - Bioadhesive strength is directly proportional to the initial contact time. It also determines the extent of swelling and interpenetration of polymers. It is not controllable for gastric systems.[44]

4) Moistening - Moistening allows the mucoadhesive polymer to spread over the surface and create a macromolecular network of sufficient size for the penetration of polymer and mucin molecules to increase the mobility of polymer chains.[47,48]

5) Presence of metal ions - Combining with charged groups of polymer and/or mucous can reduce the number of interaction sites and the strength of mucoadhesive bonding.[49,50]

C) Physiological factors

1) Mucin turnover - High mucin turnover which occurs many times is not beneficial because:

a. The high mucin turnover limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though the polymer has a good bioadhesive property.

b. High mucin turn over may produce soluble mucin molecule, thus molecule interact with the polymer, before they interact with mucin layer. Hence there will not be sufficient mucoadhesion.[27]

2) Disease state- The physicochemical property of mucus may alter during some diseased state, such as common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc.[51]

3) Renewal rate of mucosal cells– Renewal rate of mucosal cells differs considerably on the basis of types of mucosa. It limits the endurance of bioadhesive systems on mucosal surfaces.[52]

Mucoadhesive Polymers

Mucoadhesive polymers are either water soluble or insoluble, which are swellable networks, connected by cross-linking agents.[62] Various different classes of mucoadhesive polymers are shown in Fig. 8.

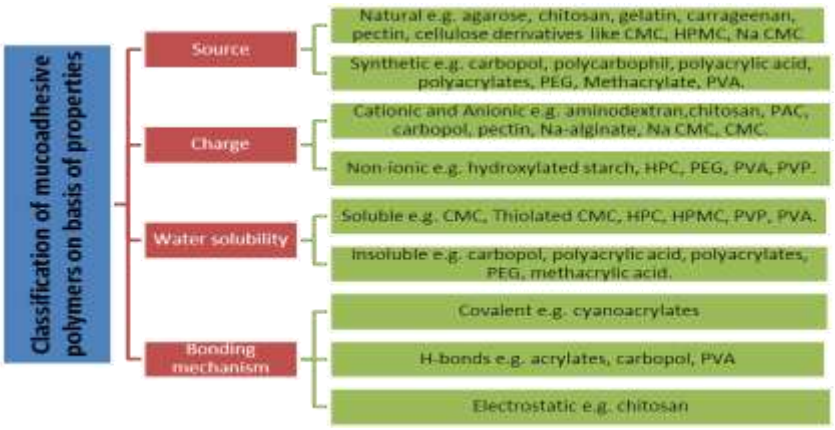

Fig. 8: An overview of mucoadhesive polymers classifications based on different ways i.e. source, charge, solubility and their mechanism of bonding.

Properties of an ideal mucoadhesive polymer[11,25,53,54]

- The polymer and its degradation products should be nontoxic, non-irritant and non-absorbable from the GIT.
- Possess high viscosity, proper degree of cross linking and proper spatial conformation of polymer is must.
- It should have site specificity and adhere rapidly to most tissues.
- It must not degrade during the shelf life of the dosage form.
- Strong H-bonding groups (-OH, -COOH) should be present in polymer for bonding with mucous membrane.
- Polymer should have strong anionic charges and high molecular weight.
- It should be sufficiently flexible to interpenetrate the mucus membrane or tissue crevices.
- It should have correct surface tension characteristics suitable for moistening of mucus surface.

1. PAA derivatives

Poly acrylic acid derivatives are polymers of acrylic acid cross linked with polyalkenyl ethers or divinyl glycol.[25,57,59] They are obtained from primary polymer particles of about 1-5 micron diameter. Each primary particle prevails as a network structure of polymer chains interconnected through cross links.[55] Carbopol, a PAA derivative, swells upto 1000 times their original volume in water and gets gelified at a pH range of 4.0 to 6.0.[25] Due to carboxylate group, repulsion occurs between the negative charges which consequently make polymer to swell and hence mucoadhesive strength of the polymer rises.[56,58]

2. Chitosan

Chitosan, a cationic semi-synthetic polymer, is obtained from chitin by deacetylation.[25] Studies have shown that chitosan can enhances absorption of hydrophilic molecules by rearrangement of protein structures associated to the intercellular junctions.[61,62] Chitosan binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Chitosan being linear gives higher polymer chain flexibility.[60]

3. Collagen

Collagen is a natural protein.[63-67] It is a tri-helical molecule.[68] Nineteen types of collagen molecules are identified.[29] Collagen has improved biocompatibility, low antigenicity and degrades less on implanting.

4. Gelatin

Gelatin is a natural water soluble protein which is normally obtained by denaturation of collagen.[70] It has good biodegradability, biocompatibility, and low antigenicity.[69] It is used as support material for gene delivery, cell culture, and more novel is use in tissue engineering. Gelatin-based systems can give zero order release of biologically active agents such as drugs, peptides and proteins.[72] It is possible to entrap bioactive compounds into pegylated liposome-gelatin gel.[71]

5. Albumin

Serum albumin was conjugated to polyethylene glycol and cross-linked to form mono-PEGylated albumin hydrogels. These hydrogels can be assessed as drug carrying tissue engineering scaffold materials.[63]

6. Alginate

Alginate is a naturally occurring linear polysaccharide. Alginate and its derivatives are used for drug delivery and tissue engineering applications due to its enhanced biocompatibility, biodegradability, low toxicity, non-immunogenicity, water solubility, comparatively low cost, better gelling properties, stabilizing properties, and high viscosity in aqueous solutions.[73-79]

7. Dextran

Dextran is a linear natural polymer of glucose cross-linked by a 1,6-glucopyranoside, and some branching of 1,3 cross-linked side chains. Its good water solubility, biocompatibility, and biodegradability are responsible for its increasing applications in pharmaceutical field.[80,83]

8. Newer second generation polymers

Newer polymers with enhanced mucoadhesive properties are now available. Mechanisms of mucoadhesion by these novel polymers like lectins, thiomers and alginate poly ethylene glycol acrylate can be seen in Fig. 9.

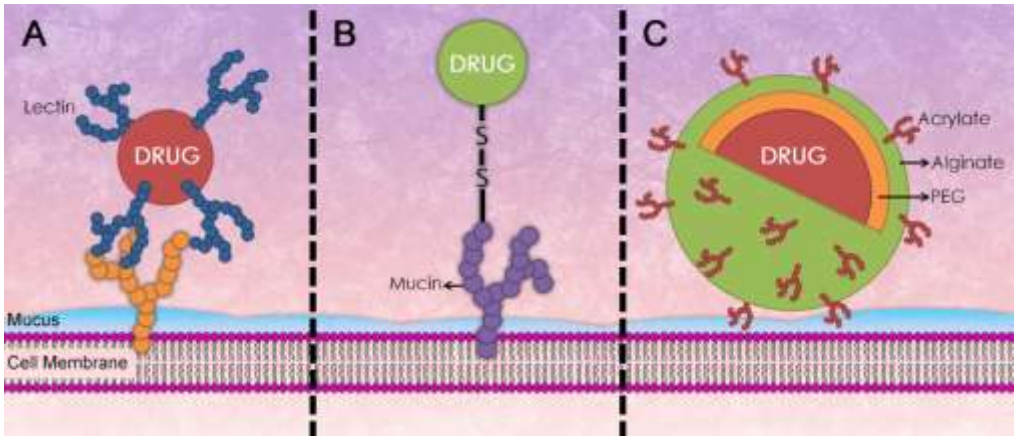

Fig. 9: Mechanisms of mucoadhesion by (A) Lectins, (B) Thiomers, (C) Alginate Poly ethylene glycol acrylate.[100] [with permission]

Their advantages are:[85,86]

• Site specificity called cytoadhesiveness.

• Not affected due to high mucus turn-over.

• Targeting of drug.

Lectins

Lectins are natural proteins useful for bio-recognition of cells and proteins.[63] They are structurally varying proteins and glycoprotein which reversibly bind to specific residues of carbohydrates. After binding to the cell, these might stay on the surface of cell or may be face endocytosis. Thus provide site specific and controlled drug release. The disadvantage is that they are immunogenic.[25]

Thiolated Polymers

Thiolated polymers are derived from water soluble polymers like polyacrylates, chitosan or deacetylated gallan gum. Based on thiol or disulphide exchange reactions or simple oxidation, disulphide bonds are formed between polymers and cysteine rich domains of mucus glycoproteins thus forming the mucus gel layer.[85] Thiomers imitate the natural mechanism of secreted mucus glycoproteins, which are covalently bound in the mucus layer through formation of disulphide bonds. Due to thiol groups, the residence time improves and thus covalent bonding is promoted with the cysteine present in mucus. The disulphide bonds might also alter the mechanism of drug release from the delivery system due to surged rigidity and cross linking.[86]

Water Soluble Resins (WSR)

POLYOX™ polymers are among the fastest-hydrating water soluble polymers used in pharmaceutical systems. This category of high molecular weight polyethylene oxide homo polymers are water soluble, high molecular weight, biocompatible and non-toxic and can also be formulated into tablets, films, gels, microcapsules and syrups.[84]

Evaluation Studies of Mucoadhesive Drug Delivery System

In vitro/*ex vivo* tests:

1. Methods of mucoadhesive strength measurement

A) Methods determining tensile strength

B) Falling liquid film method

C) Fluorescent probe method

D) Colloidal gold mucin conjugate method

2. Swelling index
3. Thumb method
4. Electrical conductance
5. Stability studies
6. Measurement of the Residence Time/ *In Vivo* Techniques

A) GI Transit using Radio-Opaque Tablets

B) Gamma Scintigraphy Technique

1 Methods of mucoadhesive strength measurement

A) Methods determining tensile strength

There is uniform distribution of stress over the adhesive joint in tensile and shear experiments, while the stress is focused at the edge of the joint in the peel strength. Thus the mechanical properties are measured through tensile and shear measure, while the peel strength measures the peeling force. Texture profile analyzer is one method used for measuring the force required to peel out bioadhesive films from cut out tissue *in vitro*.[3,4,87-89] For this, a piece of animal mucous membrane was used and it was tested for the force required to pull the formulation from a model membrane which is made from disc of mucin. The texture analyzer operates in tensile test mode and is paired with a low sliding platform which is also used to determine peel strength. On a movable platform the animal skin was placed and on top of it the bioadhesive film was placed, which was later on pulled vertically

to determine the peel strength. The different forces like detachment strength, shear strength and rupture tensile strength is shown in Fig. 10.

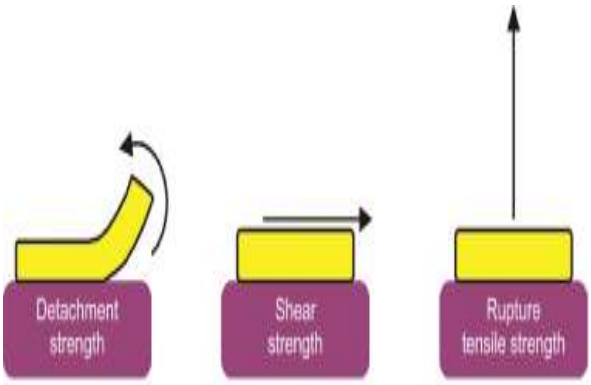

Fig. 10: Different forces evaluated in mucoadhesion test.[24] [with permission]

Another method uses modified physical balance to measure mucoadhesive strength of the dosage form as shown in Fig. 11. The apparatus is made from a modified double beam physical balance wherein the right pan is replaced by a glass slide with copper wire and additional weight, to equalize the weight on both sides of pan.

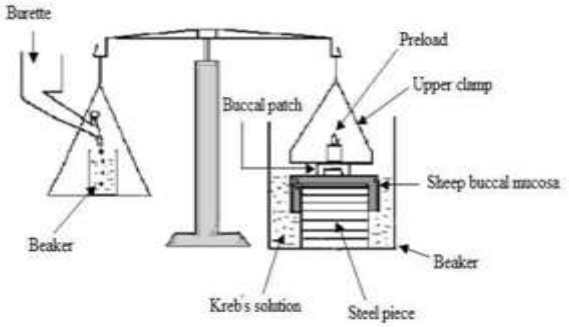

Fig. 11: Measure of mucoadhesive strength.[39] [with permission]

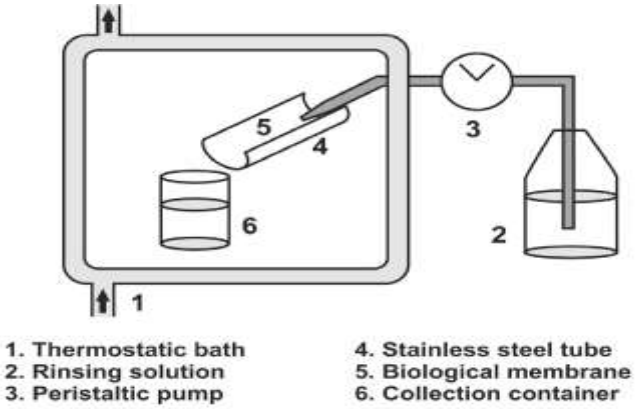

Fig. 12: Falling liquid film method.[24] [with permission]

A teflon block of specific dimensions is kept in a beaker filled with buffer of 0.1N HCl and pH 1.2, which is then placed at the bottom of the right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer is used as moistening fluid. One side of the formulation is fixed to the glass slide of the right arm of the balance and then the beaker is slowly lifted until contact between goat mucosa and mucoadhesive dosage form is established. A preload of 10 g is placed on the slide for 5 min (preload time) to establish adhesive bonding between mucoadhesive dosage form and the stomach mucosa. The preload and preload time are kept constant. At the end of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa.

The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams.

Force of Adhesion (N) = (Mucoadhesive strength * 9.81)/1000

Bond strength (N/m^2) = Force of adhesion (N)/ surface area of tablet (m^2)[3,24]

B) Falling liquid film method

In this method, as shown in Fig. 12, the mucous membrane (5) is placed in a longitudinally cut stainless steel cylindrical tube (4). This support is placed inclined in a cylindrical cell with a temperature controlled at 37°C in thermostatic bath (1). An isotonic solution (2) is pumped through the mucous membrane by peristaltic pump (3) and collected in a collection container (6). Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter.[90,91] For semi-solid systems, the non-adhered mucoadhesive can be quantified by high performance liquid chromatography.[12] This methodology allows the visualization of formation of liquid-crystalline mesophase on the mucous membrane after the flowing of the fluids and through analysis by means of polarized light microscopy.[3]

C) Fluorescent probe method

In this method, pyrene and fluorescein isothiocyanate are used to label the membrane lipid bilayer and membrane proteins respectively.[90] The mucoadhesive agents are mixed with cells and changes in fluorescence spectra are observed. This gives an indication of polymer binding and its role in polymer adhesion.[3]

D) Colloidal gold mucin conjugate method

Colloidal gold staining technique is proposed for studying bioadhesion. The method uses red colloidal gold particles, which are adsorbed on molecules of mucin to form mucin–gold conjugates. These conjugates on interaction with bioadhesive hydrogels develops a reddish tint.[3] This can be evaluated by measuring either the intensity of red color on the hydrogel surface or by measuring decline in the concentration of the conjugates through absorbance change at 525 nm.[90]

2. Swelling index

The amount of swelling is quantified in terms of % weight gained by the formulation. It is calculated using following formula:

Swelling index (S.I.) = $(W_t\text{-}W_o/W_o)$

Where, S.I = Swelling index; W_t = Weight of tablet at time t; W_o = Weight of tablet before placing in the beaker.[3]

3. Thumb method

This is used for the qualitative determination of peel adhesive strength of the polymer and is useful in the development of buccal adhesive delivery systems. The adhesiveness is measured by the strain required for pulling the thumb from the adhesive as a function of the pressure and the contact time.[11]

4. Electrical conductance

The rotational viscometer was modified to determine electrical conductance of various semi-solid mucoadhesive ointments and found that the electrical conductance was low in the presence of adhesive material.[3]

5. Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. ICH guidelines can be followed in this regard.[3]

6. Measurement of the Residence Time/ *In Vivo* Techniques

Measurements of the residence time of mucoadhesive at the application site provide quantitative information on their mucoadhesive properties.[11,101] The GI transit times of many

mucoadhesive preparations have been examined using radioisotopes and the fluorescent labeling techniques.[3]

A) GI Transit using Radio-Opaque Tablets

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time.[11]

B) Gamma Scintigraphy Technique

A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled hyaluronan based biomaterial (HYAFF) tablets. The retention of mucoadhesive-radio labeled tablets based on HYAFF polymer was found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to stomach epithelium.[3,12,92]

Dosage Forms

Tablets and Lozenges

Tablets are small, flat and oval, with a diameter of approximately 5–8 mm. The mucoadhesive tablets allow drinking and speaking without significant discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. Mucoadhesive tablets offers efficient absorption, controlled release and enhanced bioavailability of the drugs due to a high surface to volume ratio and facilitates a much more intimate contact with the mucus layer.[94]

Sprays

Oral sprays deliver drug-containing aqueous droplets to the mouth. The velocity and size of the droplets are monitored in order to ensure delivery to the oral cavity rather than to the lungs. They are capable of delivering large molecules such as insulin across the oral mucosa. Glyceryltrinitrate is a small molecule that can be rapidly delivered across the sublingual oral mucosa using a spray for angina relief. The Generex Biotechnology Corporation has developed a RapidMist® spray which is capable of delivering large molecules, such as insulin across the oral mucosa.[24]

Pastes

Pastes have been utilized in the delivery of antimicrobial agents for improved extraction socket healing after tooth extractions in patients with HIV disease and for the delivery of controlled release in oral care formulations. Mucoadhesive pastes with methylprednisolone hydrogen succinate have been characterized with carbomer polymer.[15]

Patches

Several different patch systems that adhere to the oral mucosa and are designed to deliver drugs have been developed. There are different types of oro - adhesive patches:

a) Patches with a dissolvable matrix for drug delivery to the oral cavity: These patches are longer acting than solid forms such as tablets and lozenges and can produce sustained drug release for treating oral candidiasis and mucositis. They slowly and completely dissolve during use leaving nothing to remove.

b) Non-dissolvable backing patches systems: These are for systemic drug delivery of drug and they offer protection from saliva. The patches deliver a controlled concentrated dose of the drug into the oral mucosa for 10–15 h.[95-97]

Wafers/ Films

Buccal disintegrating mucoadhesive films tend to exhibit better patient compliance than buccal tablets due to their small size, thin structure and flexibility. BioDelivery Sciences International has applied its BEMA® (BioErodible Mucoadhesive) technology to design a range of buccal transmucosal films such as Onsolis®, a buccal soluble film containing fentanyl citrate for the treatment of breakthrough pain in cancer patients who are already tolerant to opioids.[23] Similar wafer technology is already used in the treatment of migraines and it is hoped the fast dissolution of the wafers, the self-administrable nature of the technology and the high blood supply of the oral mucosa will enable fast effective treatments for many more conditions in the future.[94]

Gels

Gels are used for localized action in a site specific manner. Gels applied to the oral mucosa have been used for the delivery of systemic analgesics, anti-hypertensives and drugs for treating cardiovascular disease as well as topical delivery of antifungal agents, anti-inflammatories and mucoprotective agents to the oral mucosa.[93-96]

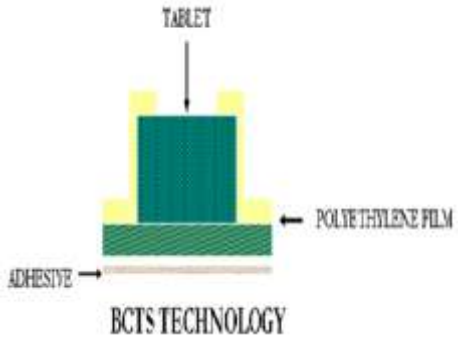

Fig. 13: BCTS technology.

Fig. 14: Mucoadhesive tablet based on effervescence.

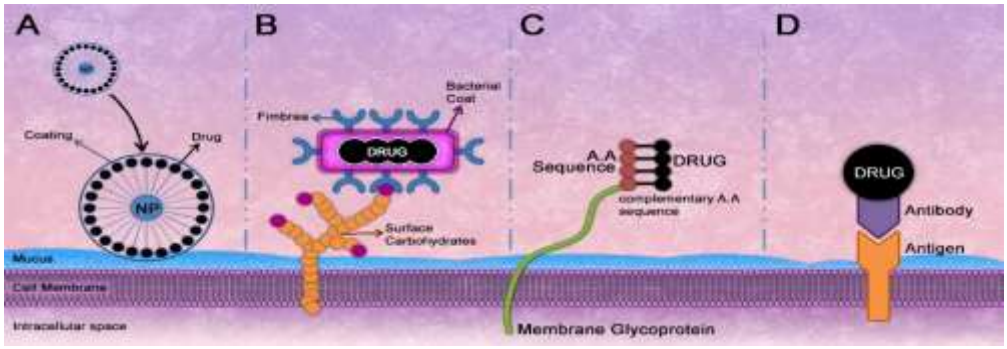

Fig. 15: Potential future novel strategies for muco-/bio-adhesive drug delivery using (A) Mucoadhesive Nanoparticles; (B) Bacterial Adhesion; (C) Altered Amino Acid Sequence; (D) Antibody mechanism.[100][with permission]

Recent innovations

Gel Forming Liquids: This type of a formulation is liquid upon instillation and undergoes a phase transition to form a viscoelastic gel in response to stimulus such as temperature, ionic strength or pH.Carbomers become more viscous upon increased pH. Gellan gum and alginate both form gel in response to increased ionic strength (particularly with Ca+2 ions). Poloxamers and smart hydrogel® (Advanced medical solution) gel at approximately body temperature.[24]

Slowly disintegrating buccal mucoadhesive plain tablet (SDBMPT): SDBMPTs are prepared by incorporating large amount of HPC. E.g. tablet having 20mg drug, 20mg HPC, 20mg CMC& 60mg lactose – mixed & compressed with a flat faced die that is 8mm in diameter. Though limitation is that it softens on extended period and lose its shape which hinders the control of disintegration over long time periods.[23]

BCTS (Buccal Covered Tablet System): It is sandwiched S-DBMP-T system between two polyethylene sheets. Upper sheet contains hole to absorb water and lower sheet is made of adhesives. It is a system which transports drug through across the mucosal membrane. Based on effervescent technology as shown in is less than pKa for a weak base hence ionization and solubilization occurs.[23]

Although several novel strategies are currently used for drug delivery using bio-and muco-adhesion strategies, the potential exists to improve these methods using other strategies such as nanoparticles, bacterial adhesion, altered amino acid sequence and antibody mechanism. These potential novel strategies for mucoadhesion can be seen in Fig. 15.[100]

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