Review on Mucoadhesive Drug Delivery System: Novel Approaches in Modern Era

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ABSTRACT

Purpose: This review article has been written with a purpose of providing extensive information regarding the theoretical considerations, mucoadhesive polymers and evaluation of mucoadhesive drug delivery system. It would be beneficial to the researchers working in this field. Approach: The anatomy and physiology of the mucosa is briefly discussed, followed by the elucidation of various theories of mucoadhesion. The properties of various mucoadhesive polymers have been discussed. The potential advantages and disadvantages have also been highlighted. Findings: The success and degree of mucoadhesion is influenced by various polymer-based properties such as the degree of cross-linking, chain length and the presence of various functional groupings. Conclusion: Mucoadhesive drug delivery system offer close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to an increase in bioavailability and greater local and systemic effects.

Key words: Bioadhesion, Buccal Mucoadhesive drug delivery, Mucoadhesive theories, Mucoadhesion, mucosa.

INTRODUCTION

Oral delivery has so far been the most common and preferred route of administration for most of the therapeutic agents. The popularity of the oral route has been attributed to the patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method, least sterility constraints, flexible design of dosage forms and generally improved shelf-life of the product.¹²

Mucoadhesive drug delivery has been a topic of interest in the design of drug delivery systems to lengthen the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the formulation with the underlying absorption surface, so as to improve and enhance the bioavailability of drug. Mucoadhesive controlled drug delivery systems are beneficial, since they give a controlled drug release over a period of time and can also be utilized for localizing the drug to a specific site in the body.³⁴

Mucoadhesive substances could also be used as therapeutic agents in their own right, to coat and protect and soothe the injured tissues (gastric ulcers or lesions of the oral mucosa) or as lubricants (in the oral cavity, eye and vagina).⁵

MECHANISM OF MUCOADHESION

Mucoadhesion is a complex process involving wetting, adsorption and interpenetration of polymer chains. Mucoadhesion is established in the following stages:

• Contact stage: Intimate physical contact between a bioadhesive/Mucoadhesive material and a membrane (wetting or swelling phenomenon).

• Consolidation stage: Penetration of the bioadhesive/Mucoadhesive into underlying the tissue or into the surface of the mucous membrane (interpenetration).⁶
**Mucoadhesion and bioadhesion**

Mucoadhesion may be defined as a state in which two components, of which one is of biological source, are joined together for prolonged periods of time by the aid of interfacial forces. ‘Bioadhesion' broadly includes adhesive interactions with any biological or biologically derived substance, whereas ‘Mucoadhesion’ is used when the bond is formed with a mucosal surface, while the term cytoadhesive means adhesion to cells. Mucoadhesive drug delivery systems are also a sub-type of gastro- retentive drug delivery systems. In the formulation of oral controlled-release dosage forms, significant benefits may follow from the use of mucoadhesive polymers providing brief adhesion between the drug delivery system and the mucous or epithelial cell surface of the alimentary canal. The bond between polymer and mucous membrane involves secondary forces, such as hydrogen bonds or Van der Waals forces. Mucoadhesives may, therefore, be regarded as a specific class of bioadhesives.

Mucoadhesive/biodhesive drug delivery system can be applied to the following systems:

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

**MUCOUS MEMBRANES**

Mucous membranes (mucosae) are the moist surfaces, lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the upper part of which is made moist usually due to the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/ stratified (e.g. in the oesophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces, the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present as either a gel layer sticking to the mucosal surface or as a soluble or suspended luminal entity. The primary components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter comprising more than 95% of its weight, making it a highly hydrated system. The mucin glycoproteins are the most important structure-forming component of the mucus gel, which provide the mucus with its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies at different mucosal surfaces, from 50 to 450 μm in the stomach, to less than 1 μm in the oral cavity. The major functions of mucus include protection and lubrication (anti adherents).

**Composition of mucus layer**

Mucus is translucent and viscous secretion which forms a thin, continuous gel layer sticking to the mucosal epithelial surface. 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.

**Functions of mucous layer**

- Mucous layer is protective because of its hydrophobicity.
- It influences the bioavailability of drugs as it acts as a barrier in tissue absorption of drugs and other substrates.
- It strongly bonds with the epithelial cell surface as a continuous gel layer.
- It plays a major role in the lubrication of the mucosal membrane and maintenance of its moisture.

**SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEM**

The common sites for mucoadhesive drug delivery systems include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract.

- The buccal cavity has a very limited surface area of around 50 cm² but the accessibility of the site makes it a preferred location for delivering therapeutic agents. Delivery through this site avoids hepatic first-pass metabolism in addition to the local treatment of the oral infections. The sublingual mucosa is relatively more permeable than the buccal mucosa; hence formulations for sublingual delivery are formulated to release the active agent immediately. The mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. Hence, the buccal cavity is more suitable for mucoadhesive drug delivery.

- Nasal cavity also offers a potential site for the designing of formulations using mucoadhesive polymers. The nasal mucosa has a surface area of about 150-200 cm² but the residence time of a particulate matter in the nasal mucosa varies between 15 and 30 min. This short time is due to the increased activity of the mucociliary layer due to stimulation by foreign particles.
Ophthalmic mucoadhesive drug delivery is also of great interest. Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents which can be reduced by delivering the drugs using ocular inserts or patches.

The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location. This can be overcome by applying the principles of mucoadhesion.

Gastrointestinal tract is also a potential site which has been explored since long for the development of mucoadhesive based formulations. The manipulation of the transit time of the delivery systems in a particular area of the gastrointestinal system by using mucoadhesive polymers has evinced a great interest among researchers around the world.

ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive delivery system offers several advantages over conventional drug delivery systems which are as follows:

- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action possible.
- Rapid absorption because of enormous blood supply and good perfusion rates.
- An alternative to oral route, whereby the drug is protected from degradation in the acidic environment of the GIT.
- Better patient compliance.
- Moreover, rapid cellular recovery and healing of the local site.
- Reduced dosing frequency.
- Shorter treatment period.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of drug administered.

DISADVANTAGES

- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH, cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may be swallowed along with the saliva and lose the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- In case of vaginal drug delivery, the drug has to be stable in the acidic vaginal pH.
- The vaginal formulation may interfere with sexual intercourse.
- The vaginal formulation may leak and cause messiness.
- The vaginal formulation may be contraindicated in case of pregnancy.
- In case of nasal formulations, the formulation may cause un easiness and blurring.
- It may get dislodged.
- In case of ocular 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 lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

THEORIES OF MUCOADHESION

Many theories have been hypothesized for explaining mucoadhesion, although the chemical and physical basis of mucoadhesion is not yet clearly understood. There are six classical theories which have resulted from studies on the performance of several materials and polymer-polymer adhesion. The contact angle and time of contact plays a significant role in mucoadhesion. Figure 1 depicts the various theories of mucoadhesion.

Wetting theory

The ability of a bioadhesive or mucous to spread and develop intimate contact with its corresponding substrate is a major factor in bond formation. The affinity between the liquid systems and the mucus membrane can be determined by measuring the contact angle. As a general rule, lower the contact angle, greater is the affinity. The contact angle should be equal or close to zero to provide adequate spreadability. Figure 2 is a schematic diagram showing influence of contact angle between the formulation and mucous membrane.

The spreadability coefficient, SAB, can be calculated from the difference between the surface energies.
$\gamma_B$ and $\gamma_A$ and the interfacial energy $\gamma_{AB}$, as indicated in equation:

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

Greater the individual surface energy of mucus and device in relation to the interfacial energy, greater is the adhesion work, $W_A$.

$$W_A = \gamma_A + \gamma_B - \gamma_{AB}$$

**Diffusion theory**

The phenomenon of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is explained by the diffusion theory. The bond strength increases with the enhancement in the degree of the penetration. Diffusion coefficient, flexibility and 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 bioadhesive bond lies in the range 0.2–0.5 μm. This interpenetration depth of polymer and mucin chains can be found out by the following equation

$$\text{The interpenetration depth, } l = (tD_b)^{1/2}$$

Where $t$ is the contact time and $D_b$ is the diffusion coefficient of the mucoadhesive material in the mucus.
adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond. Figure 3 shows interactions between polymer chains and mucus membrane.

**Fracture theory**

The most widely used theory in studies on the mechanical measurement of mucoadhesion, is the fracture theory. It analyses the force needed to separate two surfaces after adhesion is established. The work fracture has been found to be more when the polymer network fibres are longer or if the degree of cross-linking within such a system is decreased. This theory helps in the determination of fracture strength ($\sigma$) following the separation of two surfaces via its relationship to the Young’s modulus of elasticity ($E$), the fracture energy ($\varepsilon$) and the critical crack length ($L$) through the following equation. Figure 4 shows regions of mucoadhesive bond rupture.

$$\sigma = \left( \frac{E \times \varepsilon}{L} \right)^{1/2}$$

**Mechanical theory**

Mechanical theory proposes that the adhesion is due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. The roughness enhances the interfacial area available to interactions thereby aiding dissipation of energy.

**Electronic theory**

The electronic theory depends on the assumption that the bioadhesive material and the target biological material have different electronic surface characteristics. Based on this, when two surfaces come in contact with each other, electron transfer occurs in an attempt to balance the Fermi levels, resulting in the formation of a double layer of electrical charge at the interface of the bioadhesive and the biologic surface. The bioadhesive force is believed to be present due to the attractive forces across this double layer.

**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. It is one of the most widely accepted theories of bioadhesion. Table 1 indicates types of bond formed.

**FACTORS AFFECTING MUCOADHESION**

Table 2 points out various polymer related factors, environment related factors and physiological factors which affects mucoadhesion.

**POLYMER RELATED FACTORS**

**Molecular weight**

The interpenetration of polymer molecules into the mucus layer is variable, for low molecular weight polymers penetration is more than high molecular weight polymers because entanglements are favored in high molecular weight polymers.
For a linear polymer, the bioadhesive property is directly proportional to the molecular weight. For example, polyethylene glycol (PEG) having molecular weight of 20,000 has little adhesive character, whereas PEG having molecular weight of 2,00,000 has enhanced adhesive property, and PEG having molecular weight 4,00,000 has superior adhesive property. But in case of nonlinear polymer, the bioadhesiveness may or may not depend on molecular weight. This is mainly because the helical or coiled structures of such polymer may shield some of the adhesive group, which are mainly responsible for the adhesive property. For example, the adhesive property of dextran having a molecular weight of 9,50,000 is similar to that of PEG having a molecular weight of 2,00,000, due to helical structures of dextran that may shield many of adhesive groups.

**Concentration of polymer**

There is an optimum concentration for a mucoadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, the adhesive strength drops significantly because the coiled molecules become separated from the medium so the

### Table 1: Mucoadhesive–mucosa interactions

<table>
<thead>
<tr>
<th>Types of chemical bonds</th>
<th>Process of bonding</th>
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</thead>
<tbody>
<tr>
<td>Ionic bonds</td>
<td>Two oppositely charged ions attract each other via electrostatic interaction to form a strong bond (e.g. in a salt crystal)</td>
</tr>
<tr>
<td>Covalent bonds</td>
<td>Electrons are shared in pairs between the bonded atoms in order to fill the orbitals in both. These are strong bonds</td>
</tr>
<tr>
<td>Hydrogen bonds</td>
<td>Hydrogen atom covalently bonds to electronnegative atom such as oxygen, fluorine or nitrogen, carries a slight positive charge and is therefore attracted to other electronnegative atoms. The hydrogen can therefore be thought of as being shared and the bond formed is generally weaker than ionic and covalent bond</td>
</tr>
<tr>
<td>Van der Waals bonds</td>
<td>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</td>
</tr>
<tr>
<td>Hydrophobic bonds</td>
<td>Indirect bonds that occur when non polar groups are present in an aqueous solution.</td>
</tr>
</tbody>
</table>

### Table 2: Factors affecting mucoadhesion

<table>
<thead>
<tr>
<th>Polymer related factors</th>
<th>Environment related factors</th>
<th>Physiological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>pH of polymer-substrate interface</td>
<td>Mucin turnover</td>
</tr>
<tr>
<td>Concentration of polymer</td>
<td>Applied strength</td>
<td>Disease state</td>
</tr>
<tr>
<td>Flexibility of polymer chains</td>
<td>Initial contact time</td>
<td>Rate of renewal of mucosal cells</td>
</tr>
<tr>
<td>Spatial confirmation</td>
<td>Moistening</td>
<td>Concomitant diseases</td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td>Tissue movement</td>
</tr>
<tr>
<td>Hydrogen bonding capacity</td>
<td>Presence of metal ions</td>
<td></td>
</tr>
<tr>
<td>Cross linking density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charge</td>
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</tbody>
</table>
chain available for interpenetration become limited. It affects the availability of long polymer chains for penetration into the mucus layer. Thus it is important mainly for liquid and viscous drug delivery system. The importance of this factor lies in the development of strong adhesive bond with the mucus and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of polymer is too low, the number of penetrating polymer chains per unit volume of the mucous is small and the interaction between polymers and mucous is unstable.

**Flexibility of polymer chains**

For an effective bioadhesion, the polymer chain should effectively diffuse into the mucus layer. For achieving such diffusion, the polymer chain should have sufficient flexibility which depends on the viscosity and diffusion coefficient. Higher flexibility of polymer causes greater diffusion into mucus network.

**Spatial confirmation**

Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.

**Swelling or hydration**

Proper hydration to mucoadhesive polymer is essential to create macromolecular mesh of sufficient pore size and also induces mobility, which are necessary for enhancing the interpenetration.

**Hydrogen bonding capacity**

Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc.). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate and poly (methacrylic acid) as well as all their co-polymers are having good hydrogen bonding capacity.

**Cross linking density**

The cross linking density indicates the number of average molecular weight of the cross linked polymer, which determines the average pore size. When the cross linking density is higher, then the pore size becomes small, so that diffusion of water into the polymer network occurs at a lower rate, thus there is only an insufficient swelling of polymer resulting in decreased penetration of polymer into the mucin.

**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 shows superior mucoadhesive property. It has been proven that, cationic high molecular weight polymer such as chitosan possess good bioadhesive property.

**ENVIRONMENT RELATED FACTORS**

**pH of polymer-substrate interface**

pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.

**Applied strength**

While placing a buccal mucoadhesive drug delivery system, sufficient strength should be applied in order to provide a good bioadhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient long time make the polymer become bioadhesive with mucus.

**Initial contact time**

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases.

**Moistening**

Moistening is required to allow the mucoadhesive polymer to spread over the surface and create a macromolecular network of sufficient size for the interpenetration of polymer and mucin molecules to increase the mobility of polymer chains. However there is a critical level of hydration for mucoadhesive polymers characterized by optimum swelling and bioadhesion.

**Presence of metal ions**

Interaction with charged groups of polymer and/or mucous can decrease the number of interaction sites and the tightness of mucoadhesive bonding.

**PHYSIOLOGICAL FACTORS**

**Mucin turnover**

High mucin turnover is not beneficial for the mucoadhesive property because of following reasons:

- The high mucin turn over limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though it has a good bioadhesive property.
• High mucin turnover may produce soluble mucin molecule, thus molecule interact with the polymer, before they interact with mucin layer. Hence there will not be sufficient mucoadhesion.

**Disease state**

The physicochemical property of mucus may alter during some disease state, such as common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc. Thus alteration in the physiological state may affect the bioadhesive property.

**Rate of renewal of mucosal cells**

Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

**Concomitant diseases**

Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation.

**Tissue movement**

Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms.

**MUCOADHESIVE POLYMERS**

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, 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.

There are two broad classes of mucoadhesive polymers hydrophilic polymer and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties, polyvinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxymethylcellulose (SCMC) Hydroxypropyl cellulose (HPC) and other cellulose derivative. Hydrogels are the class of polymeric biomaterial that exhibit the basic characteristics of hydrogel to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

- Anionic group- Carbopol, Polyacrylates and their cross linked modifications
- Cationic group- Chitosan and its derivatives
- Neutral group- Eudragit- NE30D etc.

Table 3 contains example of various natural, synthetic, biocompatible and biodegradable polymers.

**Characteristics of an ideal mucoadhesive polymer**

- The polymer and its degradation products should be nontoxic and should be non absorbable from the GI tract.
- It should be nonirritant to the mucus membrane.
- It should preferably form a strong non covalent bond with the mucin–epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site specificity.
- It should allow easy incorporation of the drug and should offer no hindrance to its release.
- The polymers must not decompose on storage or during the shelf life of the dosage form.
- The cost of polymer should not be high so that the prepared dosage form remains competitive.

**Molecular characteristics**

| Table 3: Examples of mucoadhesive polymers.  

<table>
<thead>
<tr>
<th>Natural</th>
<th>Synthetic</th>
<th>Biocompatible</th>
<th>Biodegradable</th>
</tr>
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<tbody>
<tr>
<td>Sodium alginate, Pectin, Tragacanth, Gelatin, Carrageenan</td>
<td>Polyvinyl alcohol, Polyamides, polycarbonates, Polyalkylene glycols, Polyvinyl ethers, Esters and halides, Poly(methacrylic acid), Poly(methacrylic acid), Methylcellulose, Ethenyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl Methylcellulose, Sodium Carboxymethylcellulose</td>
<td>Esters of hyaluron an acid, Polyvinyl acetate, Ethylene glycol</td>
<td>Poly(lactides), Poly(glycolides), Poly(lactide-co-glycolides), Polycaprolactones, Polyalkyl cyanacrylates, Polyoxyesters, Polyphosphoesters, Polyhydridres, Polyphosphazenes, Chitosan, Polyethylene oxide</td>
</tr>
</tbody>
</table>
• Strong hydrogen bonding groups (-OH, -COOH).
• Strong anionic charges.
• Sufficient flexibility to penetrate the mucus network or tissue crevices.
• Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.
• High molecular weight.

NEW GENERATION OF MUCOADHESIVE POLYMER

The new generation of mucoadhesives can adhere directly to the cell surface, rather than to mucous. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. Examples of such polymers are the incorporation of l-cysteine into thiolated polymers and the target-specific, lectin mediated adhesive polymers. These classes of polymers hold promise for the delivery of a wide variety of new drug molecules, particularly macromolecules, and create new possibilities for more specific drug–receptor interactions and improved targeted drug delivery.

Co-polymers/Interpolymer complex

A block copolymer is formed when the reaction is carried out in a stepwise manner, leading to a structure with long sequences or blocks of one monomer alternating with long sequences of the other. There are also graft co-polymers, in which entire chains of one kind (e.g., polystyrene) are made to grow out of the sides of chains of another kind (e.g. polybutadiene), resulting in a product that is less brittle and more impact-resistant. Hydrogen bonding is a major driving force for inter polymer interactions.

Thiolated polymers (Thiomers)

These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Based on thiol/disulfide exchange reactions and/or a simple oxidation process disulfide bonds are formed between such polymers and cysteine-rich subdomains of mucus glycoproteins building up the mucus gel layer. So far, the cationic thiomers, chitosan–cysteine, chitosan–thiobutylamidine as well as chitosan–thioglycolic acid, and the anionic thiomers, poly (acrylic acid)–cysteine, poly (acrylic acid)–cysteamine, carboxymethylcellulose–cysteine and alginate–cysteine, have been generated. Due to the immobilisation of thiol groups on mucoadhesive based polymers, their mucoadhesive properties are 2 to 140 fold improved.

Lectins

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues (Onishi and Machida, 1999). After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis. Hence they allow a method for site specific and controlled drug delivery. The lectins have many advantages but they also have the disadvantage of being immunogenic.

MUCOADHESIVE DOSAGE FORMS

The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. The mucosa lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose, and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may include the following: Gastrointestinal delivery system, Nasal delivery system, Ocular delivery system, Buccal delivery system, Vaginal delivery System, Rectal delivery system.

EVALUATION STUDIES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

In vitro/ex vivo tests

• Methods determining tensile strength
• Methods determining shear stress
• Adhesion weight method
• Fluorescent probe method
• Flow channel method
• Mechanical spectroscopic method
• Falling liquid film method
• Colloidal gold staining method
• Viscometer method
• Thumb method
• Adhesion number
• Electrical conductance
• Swelling properties
• In vitro drug release studies
• Mucoretentability studies

In vivo methods

• Use of radioisotopes
• Use of gamma scintigraphy
• Use of pharmacoscintigraphy
• Use of electron paramagnetic resonance (EPR) oximetry
• X - ray studies
• Isolated loop technique

In vitro method
**Methods determining tensile strength**

In tensile and shear experiments, the stress is uniformly distributed over the adhesive joint, whereas in the peel strength stress is focused at the edge of the joint. Thus tensile and shear measure the mechanical properties of the system, whereas peel strength measures the peeling force.

Texture profile analyzer is a commercial instrument which is used to measure the force required to remove bioadhesive films from excised tissue in vitro. For this test, a piece of animal mucous membrane was taken and tested for the force required to take away the formulation from a model membrane which consists of disc composed of mucin. The texture analyzer, operating in tensile test mode and coupled with a sliding lower platform, was also used to determine peel strength of similar formulations. 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. Figure 5 and 6 are diagrams of texture profile analyzer and determination of peel strength.

**Methods determining shear stress**

The measurement of the shear stress gives a direct correlation to the adhesion strength. In a simple shear stress measurement based method two smooth, polished plexiglass boxes are selected; one block is fixed with adhesive Araldite® on a glass plate, which is fixed on leveled table. The level is adjusted with the spirit level. To the upper block, a thread is tied and the thread is passed down through a pulley, the length of the thread from the pulley to the pan was 12 cm. At the end of the thread a pan of fixed is attached. More weights can be added to it. A recent method involves the measurement of mucoadhesion by use of a stainless steel rotating cylinder which is coated with freshly excised porcine intestinal mucosa to which polymer discs were attached. The cylinder is placed in a dissolution apparatus and rotated at 125 RPM. It is analysed every 30 mins for the attachment of the polymers discs.

**Falling liquid film method**

In this method the mucous membrane is placed in a stainless steel cylindrical tube, which has been longitudinally cut. This support is placed inclined in a cylindrical cell with a temperature controlled at 37°C. An isotonic solution is pumped through the mucous membrane and collected in a beaker. Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a counter. For semi-solid systems, the non-adhered mucoadhesive can be quantified by high performance liquid chromatography. 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.

**Fluorescent probe method**

In this method the membrane lipid bilayer and membrane proteins are labeled with pyrene and fluorescein isothiocyanate, respectively. The cells are mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gives an indication of polymer binding and its influence on polymer adhesion.

**Flow Channel method**

The method was conducted in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesives polymers for oral use. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescence isothio-
nate, respectively. The cells were then mixed with candidate bioadhesives and the change in fluorescence spectra was monitored. This gave an indication of polymer binding and its influence on polymer adhesion.

**Swelling index**

The extent of swelling can be measured in terms of % weight gain by the dosage form. The swelling index is calculated using following formula.

\[
\text{Swelling Index (S.I)} = \frac{W_t - W_o}{W_o}
\]

Where, S.I = Swelling index
Wₜ = Weight of tablet at time t
Wₒ = Weight of tablet before placing in the beaker

**Colloidal gold staining method**

Colloidal gold staining technique is proposed for the study of bioadhesion. The technique employs red colloidal gold particles, which are adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesives hydrogels develops a red color on the surface. This can be quantified by measuring either the intensity on the hydrogel surface or the conjugates at 525 nm.

**Viscometric method**

A simple viscometric method is used to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15% w/v porcine gastric mucin dispersion in 0.1M HCl (pH 1) or 0.1M acetate buffer (pH 5.5) is measured with a Brookfield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion are calculated.

**Thumb method**

This is a very simple test used for the qualitative determination of peel adhesive strength of the polymer and is useful tool in the development of buccal adhesive delivery systems. The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time.

**Adhesion number**

Adhesion number for mucoadhesive microspheres is determined as the ratio of the number of particles attached to the substrate to the total number of applied particles, expressed as a percentage. The adhesion strength increases with an increase in the adhesion number.

**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.

**Mucoadhesive Strength**

Mucoadhesive strength of the dosage form can be measured on the modified physical balance. The apparatus consists of a modified double beam physical balance in which the right pan is replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon® block of fixed diameter and height is fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This is kept in beaker filled with buffer media 0.1N HCl pH 1.2, which is then placed below right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer media 0.1N HCl pH 1.2 can be used as moistening fluid. The one side of the dosage form is attached to the glass slide of the right arm of the balance and then the beaker is raised slowly 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 adhesion bonding between mucoadhesive dosage form and goat or rat stomach mucosa. The preload and preload time are kept constant. After the completion 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. Figure 7 is mucoadhesion test assembly.

\[
\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive Strength} \times 9.81}{1000} \frac{\text{Force of Adhesion (N)}}{\text{Surface area of tablet (m}^2\text{)}}
\]

**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.

**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. The GI transit times of many mucoadhesive preparations have been examined using radioisotopes and the fluorescent labeling techniques.
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. Feces collection (using an automated feces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesives labeled with Cr-51, Tc-99m, In-113m, or I-123 have been used to study the transit of the tablets in the GI tract.

Gamma Scintigraphy Technique

Distribution and retention time of the mucoadhesive tablets can be studied using the gamma scintigraphy technique. A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled HYAFF tablets. Dimensions of the stomach part of the sheep can be outlined and imaged using labeled gellan gum, and the data collected are subsequently used to compare the distribution of radio labeled HYAFF formulations. 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. The combination of the sheep model and the gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomach mucoadhesive tablets. Table 4 contains information about some commercially available mucoadhesive drug delivery systems.

Table 4: Commercial mucoadhesive drug delivery system.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mucoadhesive polymers</th>
<th>Application site</th>
<th>Name and form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone acetonide</td>
<td>Hydroxypropylcellulose, Carbopol934</td>
<td>Oral cavity</td>
<td>Attach tablet</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Synchron (modified HPMC)</td>
<td>Buccal</td>
<td>Susadrin tablet</td>
</tr>
<tr>
<td>Prochlorperazine maleate</td>
<td>Ceronia, Xanthum Gum</td>
<td>Buccal</td>
<td>Buccastem tablet</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Hydroxypropyl cellulose</td>
<td>Oral cavity</td>
<td>Salcoat powder spray</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Sodium CMC, pectin, and gelatin in polyethylene mineral oil base</td>
<td>Oral cavity</td>
<td>Orabase gel</td>
</tr>
<tr>
<td>Aluminium hydroxide</td>
<td>Sodium CMC, Pectin, and gelatin in polyisobutylene spread onto polyethylene film</td>
<td>Oral cavity</td>
<td>Orahesive bandage</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>Oral cavity</td>
<td>Vaginal</td>
<td>Replen gel</td>
</tr>
<tr>
<td>Polyacrylic acid</td>
<td>Gastrointestinal ulcers</td>
<td>Vaginal</td>
<td>Sucralfate</td>
</tr>
<tr>
<td>Sucrose octasulfate</td>
<td></td>
<td>Vaginal</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

The mucoadhesive drug delivery system is a very promising approach for delivering the drugs which have narrow absorption window at the target site to maximize their usefulness. With the introduction of a large number of new drug molecules from drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules. Improvements in mucoadhesive based oral delivery and, in particular, the development of novel, highly-efficative and mucosa compatible polymers, are creating new commercial and clinical opportunities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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