ABSTRACT

Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Mucoadhesion is currently explained by five theories: electronic, adsorption, wettability, diffusion and fracture. The process of mucoadhesion involving a polymeric drug delivery system is a complex one that includes processes such as wetting, adsorption and interpenetration of polymer chains. Mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. As such, mucoadhesive systems have found wide use throughout many mucosal covered organelles for active ingredients delivery for local or systemic effect. The administration of drugs by the buccal route has several advantages over per oral administration such as quick action, improved patient compliance particularly with paediatric & geriatric patient. This review article aims to provide an overview of the various aspects of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, and finally various mucoadhesive drug delivery systems.

KEYWORDS: Bioadhesive, Mucoadhesive Polymers, Mucoadhesive Drugs.

INTRODUCTION

The concept of mucoadhesion was introduced in the field of controlled release drug delivery systems in the early 1980s.[1,2] Thereafter, several researchers have focused on the
investigations of the interfacial phenomena of mucoadhesive hydro gels with the mucus. For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Hence a bacterial attachment is to tissue surfaces, and mucoadhesion can be modelled after the adherence of mucus on epithelial tissue. Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane. By this definition, the mucosal routes for drug delivery are:

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

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption.\[3\] A number of relevant Mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1-5%), owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.\[4\]

MUCOADHESION
The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces.\[5\] In biological systems, bioadhesion can be classified into 3 types:

• Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.
• Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio-film formation on prosthetic devices and inserts.
• Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.\[^6\]

**MECHANISMS OF MUCOADHESION**

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water.\[^7\]

Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Figure 1). The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.\[^8\] In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motions can contribute to this contact, but there is little evidence in the literature showing appropriate adhesion. Additionally, an undesirable adhesion in the oesophagus can occur. In these cases, mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier.\[^9\]

In the consolidation step (Figure 1), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.\[^9\] Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds.\[^9\] For this to take place the mucoadhesive device has features favouring
both chemical and mechanical interactions. For example, molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induct its spread spread throughout the mucus layer, can present mucoadhesive properties.\[^{10}\]

According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulations or highly hydrated forms.\[^{9}\]

**Figure 1:** Two steps of mucoadhesion process.

**Figure 2:** Dehydration theory of mucoadhesion.
ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS\textsuperscript{[11]}

- Prolongs the residence time of the dosage form at the site of absorption.
- To avoid the first pass metabolism.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Drug is protected from degradation in the acidic environment in the GIT.
- Improved patient compliance and ease of drug administration.
- Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug.

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS\textsuperscript{[11]}

- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.

MUCOADHESION THEORIES

Various theories exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a limited number of the diverse range of interactions that constitute the bioadhesive bond.\textsuperscript{[12]} However five main theories can be distinguish.

- Wetting theory
- Electronic theory
- Fracture theory
- Adsorption theory
- Diffusion theory

Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity. The contact angle should be equal or close to zero to provide adequate spreadability.\textsuperscript{[10]} The
spreadability coefficient, S\(AB\), 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 (1).\(^9\)

\[
S_{AB} = \gamma_A + \gamma_B - \gamma_{AB}
\]  

(1)

The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, \(W_A\), i.e. the greater the energy needed to separate the two phases.\(^9\)

\[
W_A = \gamma_A + \gamma_B - \gamma_{AB}
\]  

(2)

**Electronic theory\(^{[7,13]}\)**

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.

**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. For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxyl groups.\(^{[8,16,7,9]}\) Such forces have been considered the most important in the adhesive interaction phenomenon\(^9\) because, although they are individually weak, a great number of interactions can result in an intense global adhesion.\(^{[10]}\)

**Fracture theory**

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

\[
\sigma = (E \times \varepsilon/L)^{1/2}
\]  

(3)

where \(\sigma\) is the fracture strength, \(\varepsilon\) fracture energy, \(E\) young modulus of elasticity and \(L\) the critical crack length.\(^{[17]}\)

**DIFFUSION THEORY**

The concept of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is supported by the diffusion theory. The bond strength increases
with the increase in the degree of the penetration.\textsuperscript{[18]} This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time.\textsuperscript{[8,16,7,9]} According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2-0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by equation.

\[ l = (\tau D_b)^{1/2} \]

where \( \tau \) is the contact time and \( D_b \) is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size.\textsuperscript{[10]}

![Figure 3: Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus.](image)

**Mechanical theory**

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.\textsuperscript{[19,9]} It is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables.\textsuperscript{[7]}

**MUCOADHESIVE POLYMERS PROPERTIES**

1. It must be loaded substantially by the active compound.
2. Swell in the aqueous biological environment of the delivery–absorption site.
3. Interact with mucus or its components for adequate adhesion.
4. When swelled they allow, controlled release of the active compound.
5. Be excreted unaltered or biologically degraded to inactive, non-toxic oligomers.
6. Sufficient quantities of hydrogen bonding chemical groups.
7. Possess high molecular weight.
8. Possess high chain flexibility.
9. Surface tension that will induce spreading into mucous layer.[32]

**POLYMERS USED FOR MUCOADHESIVE DRUG DELIVERY**[20]

These polymers are classified as,

**Hydrophilic polymers**
Contains carboxylic group and possess excellent mucoadhesive properties. These are,

- **PVP** (Poly vinyl pyrrolidine)
- **MC** (Methyl cellulose)
- **SCMC** (Sodium carboxyl methyl cellulose)
- **HPC** (Hydroxyl propyl cellulose)

**Hydrogels**
These swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge

- **Anionic polymers** - carbopol, polyacrylates
- **Cationic polymers** - chitosan
- **Neutral/ non-ionic polymers** - eudragit analogues

**FACTORS AFFECTING MUCOADHESION**[22]
The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

**Polymer Based Factors**
1. Molecular weight of the polymer, concentration of polymer used of polymer chain.
2. Swelling factor stereochemistry of polymer.

**Physical Factors**
pH at polymer substrate interface applied strength, contact time.
Physiological Factors
Mucin turnover rate diseased state.

MUCOADHESIVE DOSAGE FORM

Tablets
Tablets are small, flat and oval, with a diameter of approximately 5–8 mm. Unlike the conventional tablets, mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, for example, it offers efficient absorption 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. This mucoadhesive tablet allowed patients to eat and speak without discomfort and caused no irritation, bad taste or pain.

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

Films
Mucoadhesive films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Thin strips of polymeric films, capable of loading up to 20 mg of drugs, dissolve on the tongue in less than 30 s and deliver drugs (which are able to cross the permeability barrier) directly to the blood supply for rapid treatment of conditions such as impotence, migraines, motion sickness, pain relief and nausea.

Gels and ointments
Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of
application has been overcome by using mucoadhesive formulations. Certain mucoadhesive polymers, for example, sodium carboxymethylcellulose,\textsuperscript{[34]} carbopol,\textsuperscript{[35]} hyaluronic acid,\textsuperscript{[36]} and xanthan gum,\textsuperscript{[37]} undergo a phase change from liquid to semisolid. This change enhances the viscosity, which results in sustained and controlled release of drugs. Hydrogels are also a promising dosage form for buccal drug delivery.\textsuperscript{[38]} Gels applied to the oral mucosa have been trialled for the delivery of systemic analgesics, antihypertensive and drugs for treating cardiovascular disease as well as topical delivery of antifungal agents, anti-inflammatory and mucoprotective agents to the oral mucosa.\textsuperscript{[19]}

**Sprays**\textsuperscript{[30]}

Spray which is 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.

**Pastes**\textsuperscript{[31]}

Pastes have been utilised 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 triclosan in oral care formulations. Pastes are also being used for the local delivery and retention of slow release minocycline in the gingival crevice surrounding teeth in the treatment of periodontal disease. Liposomes have been investigated as drug delivery carriers both as a solution and in a paste formulation.

**Table 1: Shows Some Commercially Available Oral Mucoadhesive Drug Delivery Systems**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Type of release</th>
<th>Product Name</th>
<th>Manufacture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl citrate</td>
<td>Lozenges</td>
<td>Quick</td>
<td>Actiq</td>
<td>Cephalon</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>Quick</td>
<td>Fentora</td>
<td>Cephalon</td>
</tr>
<tr>
<td></td>
<td>Film</td>
<td>Quick</td>
<td>Onsolis</td>
<td>Meda Pharmaceutical Inc.</td>
</tr>
<tr>
<td>Buprenophine Hcl</td>
<td>Tablet</td>
<td>Quick</td>
<td>Subutex</td>
<td>Reckitt Benckiser</td>
</tr>
<tr>
<td>Buprenophine Hcl and naloxone</td>
<td>Tablet</td>
<td>Quick</td>
<td>Subutex</td>
<td>Reckitt Benckiser</td>
</tr>
<tr>
<td>Proclorperazine</td>
<td>Tablet</td>
<td>Controlled</td>
<td>Buccasten</td>
<td>Reckitt Benckiser</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Tablet</td>
<td>Controlled</td>
<td>Striant SR</td>
<td>Columbia pharmaceutical</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Tablet</td>
<td>Quick</td>
<td>Nitrostate</td>
<td>W lambert- pDavis</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>Quick</td>
<td></td>
<td>Pfizer pharmaceuticals</td>
</tr>
<tr>
<td>Glyceryltrinitrate</td>
<td>Spray</td>
<td>Quick</td>
<td>Nitromist</td>
<td>NovaDel</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Chewing gum</td>
<td>Quick</td>
<td>Nicorette</td>
<td>GSK consumer health</td>
</tr>
<tr>
<td></td>
<td>Lozenge</td>
<td>Quick</td>
<td>Nicotinelle</td>
<td>Novartis consumer</td>
</tr>
</tbody>
</table>
MARKETED FORMULATIONS

CONCLUSION

Beside delivery drug to the body, a drug delivery system with a aim to improve patient compliance and convenience are more important. Mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in a high drug flux through the absorbing tissue. Studies on mucoadhesive systems have focused on a broad array of aspects. It is a growth area whose goal is the development of new devices and more “intelligent” polymers, as well as the creation of new methodologies that can better elucidate the mucoadhesion phenomenon. With the appropriate technologies, delivery techniques and the choice of the polymer for the oral mucosa could, in the future, be utilized for the treatment of many diseases both mucosal and systemic and the catalogue of drugs which can be delivered via the mucosa could be greatly increased.

REFERENCE


