A Mini Review on Mucoadhesion

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ABSTRACT

The concept of mucoadhesion was started in early 1980’s with the aim of controlled delivery of drugs. Mucoadhesion is simply defined as the adhesion between two materials, in which one is the mucosal surface and the another one is the mucoadhesive dosage form. In the recent decades, mucoadhesive drug delivery system draw the attention in the gastroretentive delivery system. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time. Mucoadhesive dosage forms are designed to increase the retention of the drug/dosage form at the application site, to provide a controlled release of drug for increased curative consequence. The medications which have local action or those which have maximum absorption in gastrointestinal tract require increased duration of stay in GIT. Mucoadhesive drug delivery systems were prepared by using either natural or synthetic polymers, which is interacting with the mucous layer and used to prevail over the physiological barriers for extended drug delivery. The mucoadhesive ability of a dosage form is depending upon variety of factors, such as the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. This review article aims to provide an overview of the various theories of mucoadhesion, properties of mucoadhesive materials, methods to study the mucoadhesion, and finally various mucoadhesive dosage forms.

INTRODUCTION

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. Good (Good, 1976) defined bioadhesion as the state in which two materials, at least one of which being of a biological nature, are held together for an extended period of time by interfacial forces. It is also defined as the ability of a material (natural or synthetic) to adhere to a biological tissue for an extended period of time. The bioadhesion is classified into four types through i). normal cell to another normal cell, ii). cell with a foreign substance, iii). normal cell to a pathological cell, iv). adhesive to a biological substrate.

In drug delivery, the term bioadhesion refers to adhesion of the drug at a particular biological site. The site may be epithelial cell and mucous layer. It the adhesion is in mucous layer it is called as mucoadhesion. Mucoadhesion is a relationship between a mucous layer and a polymer of either natural or synthetic.

In mucoadhesion the water-soluble polymers adhere on hydration and then it can target the drug to a particular site of the body for a long period of time. The mucus layers are present in various parts of
the body including the gastrointestinal tract (GIT), urogenital tract, airways, ear, nose and eye. So the mucoadhesive drug delivery systems may include buccal, sublingual, vaginal, rectal, nasal, ocular and gastrointestinal delivery systems.

**Theories of mucoadhesion**

Researchers identified a number of theories about the mechanism of mucoadhesion, only six theories mainly describe the mechanisms of mucoadhesion such as electronic, adsorption, wetting, diffusion, mechanical and fracture theory (Ahuja et al., 1997).

**Electronic theory**

Electronic theory describe that the electrons transfer from mucous layer to mucoadhesive and vice-versa caused by the difference in their electron structures, which form a double layer of electrical charges, leads to attraction.

**Adsorption theory**

Adsorption theory explains that the attraction is by molecular bonding of hydrogen and vanderwaals bonds and it is more than the force caused by electronic theory.

**Wetting theory**

Wetting theory related with the interfacial energy caused by the swelling of mucoadhesive and its spread on the mucous layer.

**Diffusion theory**

Diffusion theory is the interpenetration and entanglement of polymer chains (Kaur and Smitha, 2002) of mucoadhesive and proteins present in the mucous layer.

**Mechanical theory**

Mechanical theory assumes that the adhesion occurs by interlocking of an adhesive to a rough surface. The rough surface has more surface area for the interaction.

**Fracture theory**

Fracture theory is the force needed to separate the adhesion of mucous and mucoadhesive. The failure occurs only at the weakest point, which is typically a cohesive failure that occurs on either side of adhering surfaces.

All of these theories are not giving the complete mechanism of the mucoadhesion. The mucoadhesion may occur by the combination of all theories (Solomonidou et al., 2001). While on mucoadhesion, first, wetting theory applies (polymer gets wet with mucous layer and swells), then, electronic and adsorption theory applies (formation of bonds and transfer of electrons between the polymer and mucous), then, diffusion theory applies (interpenetration of proteins and polymers), and again electronic and adsorption theory (formation of non-covalent and covalent bonds).

**Material properties of mucoadhesives**

Material properties of mucoadhesives contribute good adhesiveness based on one or multiple theories. These properties make the mucoadhesives to swell and form the bonds with mucous layer.

**Swelling**

Swelling is most important in the mucoadhesion, as it is related to the polymers wetting and spreading over the mucous. This spreading is controlled by the interfacial energies of the mucoadhesive and mucous layer, which governs the formation of bonds. But the same time deterioration of the mucoadhesion also possible, when the polymers gets overhydrated and becomes slippery mucilage, which degrades the mucoadhesion.

**Molecular bonding**

The formation of covalent and non-covalent bonds with the mucous layer is based on the molecules present in the mucoadhesives. These bonds will provide good adhesion based on the electronic and absorption theory. Non-covalent bonds are formed immediately when the mucous layer and mucoadhesives get contact, but they are weaker than the covalent bonds, which take more time to create, therefore non-covalent bonds are not having much mucoadhesion. The delay in time for the formation of covalent bonds results the more mucoadhesion at the particular site this leads to extended release of drug at the site. That’s why the researchers are synthesizing the mucoadhesive polymers with covalent bonds even though it took more time for the formation.

**Spatial conformation**

The diffusion co-efficient and the chemical potential gradient of the interacting macromolecules play a vital role in the interpenetration of the mucous and mucoadhesive chains. The chain length, which is going to penetrate into the mucous is based on the mobility and flexibility of the mucoadhesive chains. Spatial conformation is a time-dependent phenomenon, is most important in the interpenetration of mucous–mucoadhesive chains (Junginger, 2008).

**Rheological properties**

The rheological behavior of the material will be changed by the entanglement of chains and the molecular bonding between the mucous and the mucoadhesive. The change in rheological proper-
Table 1: *In-vitro* methods to study the release rate of mucoadhesives.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Apparatus</th>
<th>Testing medium</th>
<th>Agitation conditions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Tablet</td>
<td>Rotating basket immersed in a beaker</td>
<td>1/15M PB pH 7.38 (50mL)</td>
<td>100 rpm</td>
<td>(Ishida et al., 1981)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Tablet</td>
<td>Tablet submerged in a flask</td>
<td>Chloroform (50mL)</td>
<td>Magnetic stirring</td>
<td>(Smart, 1991)</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Ointment</td>
<td>Nessler’s tube</td>
<td>Normal Saline</td>
<td>Mechanical shaker</td>
<td>(Bremecker et al., 1984)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Tablet</td>
<td>Dissolution apparatus</td>
<td>0.1 N HCl</td>
<td>50 rpm</td>
<td>(Ponchel et al., 1987)</td>
</tr>
<tr>
<td>Cetylpyridinium chloride</td>
<td>Tablet</td>
<td>Paddle method</td>
<td>Mc Ilvaine buffer pH-6.6 (50 mL)</td>
<td>250 rpm</td>
<td>(Collins and Deasy, 1990)</td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td>Tablet</td>
<td>USP Paddle device</td>
<td>Isotonic PBS</td>
<td>70 rpm</td>
<td>(Bottenberg et al., 1989)</td>
</tr>
<tr>
<td>Propranolol HCl</td>
<td>Tablet</td>
<td>USP rotating basket method</td>
<td>PB, pH 6.8</td>
<td>50 rpm</td>
<td>(Kislal and Celebi, 1992)</td>
</tr>
<tr>
<td>Propranolol HCl Disc</td>
<td>Disc</td>
<td>USP type-II Apparatus</td>
<td>PB, pH 3.5/6.8</td>
<td>75 rpm</td>
<td>(Chen et al., 1992)</td>
</tr>
<tr>
<td>Verapamil HCl</td>
<td>Tablet</td>
<td>Tablet kept in a cylindrical flask with teflon block</td>
<td>Isotonic PB, pH-6.6 (100 mL)</td>
<td>50 rpm</td>
<td>(Gupta et al., 1994)</td>
</tr>
<tr>
<td>Triamcinoloneacetoneide (Encapsulated)</td>
<td>Ointment</td>
<td>Franz diffusion cell</td>
<td>PBS, pH-7.2</td>
<td>Magnetic stirring</td>
<td>(Sveinsson and Holbrook, 1993)</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Disc</td>
<td>Modified USP type-II method</td>
<td>Dis. water (500 mL)</td>
<td>100 rpm</td>
<td>(Garcia-González et al., 1993)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Tablet</td>
<td>USP dissolution apparatus-I</td>
<td>Methanol: water (3:7)</td>
<td>-</td>
<td>(Save and Venkitachalam, 1994)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Patch</td>
<td>Patches affixed to plexiglass sample blocks and submerged in flask</td>
<td>PB, pH-7</td>
<td>-</td>
<td>(Guo, 1994)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Tablet</td>
<td>Dissolution test apparatus (JP XII)</td>
<td>Dis. water (1000 mL)</td>
<td>150 rpm</td>
<td>(Miyazaki et al., 1994)</td>
</tr>
<tr>
<td>Isosorbidedinitrate Film</td>
<td>Film</td>
<td>Dissolution test apparatus (JP XII)</td>
<td>Buffered Clark-Lubs solution (500 mL)</td>
<td>100 rpm</td>
<td>(Danjo et al., 1994)</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>Tablet</td>
<td>Tablet kept in a cylindrical flask with teflon block</td>
<td>Isotonic PB (pH-6.6)</td>
<td>50 rpm</td>
<td>(Ahuja et al., 1995)</td>
</tr>
</tbody>
</table>
ties will reflect on the degree of interaction between mucous and mucoadhesive (Junginger, 2008). High degree of interaction show good mucoadhesion between the mucous and mucoadhesive systems. In many cases the viscosity of the system is more than the sum of individual viscosities of the mucous and mucoadhesive. This is called rheological synergism (Madsen, 1998). If we got more rheological synergism means, the molecular bonding and the chain entanglement is more, which results good mucoadhesion property.

Cohesiveness

The various dosage forms of mucoadhesive drug delivery in the GIT, like tablets, capsules, pellets, granules, micro & nanoparticles, have been studied both in-vitro and in-vivo. Other type of connection betwixt cohesiveness and mucoadhesive ability was also carried out in which the mucoadhesiveness of various polymers were investigated (Hägerström et al., 2000). It proves that more interaction between the polymer and the mucin will not make the gel strengthened and becomes weak, because it affects the polymer’s internal cohesive composition.

METHODS OF BIOADHESION STUDY

There are numerous methods have been reported for the bioadhesion study (Ahuja et al., 1995). They have not only studied the screening of mucoadhesives, but also the mechanisms of mucoadhesion. These tests are also important while designing of mucoadhesive drug delivery system to ensure the compatibility, mechanical and physical stability, bioadhesive bond strength and the surface analysis.

The methods used are categorized into in-vitro and in-vivo.

In-vitro methods

Most of the in-vitro studies are performed to measure either shear stress or tensile strength. Shear stress is used to determine, only the bioadhesiveness, because no other standard test is available to check the bioadhesion.

(a) Tensile strength

Tensile strength is the force needed to remove the polymer and a mucous membrane. Tensile strength testers or modified balances are used to measure the tensile strength. A modified tensiometer, which is, used to find out the force needed to detach the mucoadhesive from the biological membrane. The mucoadhesive polymer placed between the two mucosal tissues, which are exposed outside by tied on rubber stopper of glass vial. The force required to detach these two mucosal tissues was recorded. This study was a platform to find out the effect of hydrophobicity, charge density, and experimental conditions such as ionic strength, pH, applied pressure and mucolytic agents on bioadhesion (Park and Robinson, 1985).

(b) Shear strength

The shear stress is the force required to slide the bioadhesive from the mucous membrane. It is estimated by Wilhelmy plate method (Smart et al., 1984). In this, a glass plate is tied with a physical balance and dipped in a temperature controlled mucous sample. The force required to pull the plate from the solution is estimated under constant experimental conditions. Shearing stickiness apparatus also used to calculate the shear strength.

(C) Other in-vitro methods

1. Adhesion weight method

Smart and Kellaway (1982) developed a method, in which, ion-exchange resin suspension is flowed over the mucosal surface of a section of guinea-pig intestine and the weight of the adherent particles determined. But this method had limited value because the reproducibility of the data is not to satisfactory.

2. Fluorescent probe method

Fluorescent probe method was based on interaction of polymer with the conjunctival epithelial cell membrane using fluorescent probes (Park and Robinson, 1984). Pyrene and fluorescein isothiocyanate, were used for this. The cells were then mixed with candidate mucoadhesives and the changes in fluorescence spectra were recorded.

3. Flow channel method

In flow channel method a thin glass tube filled with 2% v/v bovine submaxillary mucin solution which is maintained at 37°C (Mikos and Peppas, 1990). A part of a bioadhesive polymer is placed on the mucin solution and the humid air was passed through the glass tube, then the static and dynamic behavior of the polymer was recorded at regular time intervals.

4. Mechanical Spectroscopic method

Mechanical spectroscopy is used to find out the rheological behaviour of the mucous gel and its interactions. In some cases, the formulations show same bioadhesive strength in in-vitro, may show dissimilar bioadhesive strength in-vivo (Ahuja et al., 1997). Its because of dissimilar erosion resistance or excessive swelling of the formulations. Excessive swelling may produce slippery surface.

5. Falling liquid film method

In a falling liquid film method, tygon tube was filled with small intestine segments of rats. The particles
adhered to the intestinal surface is determined by passage of particle suspension through the intestinal surface. By using the same principle, the adhesion strength of polymers also determined (Rao and Buri, 1989).

6. Colloidal gold staining method

In this, colloidal gold particles were used to determine the bioadhesion (Park, 1989). While mucin and gold conjugates interacted, the bioadhesives develops red colour over the surface. Then the interaction is measured by the intensity of red colour on the hydrogel surface.

7. Viscometric method

Normal viscometric method also used calculate the bioadhesive strength of the polymer. Brookfield viscometer is used to measure the viscosities of porcine gastric mucin (15% w/v) dispersions in either 0.1 N HCl or 0.1 N acetate buffer, with and without polymer. The differences in viscosities were used to calculate the bioadhesion (Ahuja et al., 1997).

8. Thumb test

Thumb test is the simplest method to find the mucoadhesion. The adhesiveness is quantitatively measured by the pressure required to pull the thumb from the adhesive with respect to contact time (Ahuja et al., 1997). The thumb test is an incontrovertible proof, but it gives us some information about the mucoadhesion potential.

9. Adhesion number

The adhesion number is used to calculate the mucoadhesion, when mucoadhesives are available as particles (Ahuja et al., 1997).

10. Electrical conductance

Electrical conductance is used to test mucoadhesive ointments (Bremecker et al., 1984). The adhesion of carbopol, orabase, methyl cellulose, cudispert, and guar gum to an artificial biomembranes with artificial saliva was measured by electrical conductance. The time, which was influenced by artificial saliva, the sample, and the artificial membrane, were measured. If the conductance is low the adhesion was good.

In vivo methods

Various in-vivo methods were used to measure bioadhesive strength. Measurement of retention time of mucoadhesive at the application site is the most commonly reported method. The radioisotopes such as Cr, $^{99m}$ Tc were used to determine the GI transit times of bioadhesives.

EVALUATION OF MUCOADHESIVE DOSAGE FORMS

Bioadhesive strength and release rate are the two common parameters involved in the evaluation of mucoadhesive drug delivery systems.

Bioadhesive strength

The bioadhesive strength was measured by using a modified 2-arm balance with rabbit buccal mucosa (Balasubramanian et al., 2019; Selvaraj et al., 2019). Modified double beam physical balance was used as an apparatus to calculate the bioadhesive strength. The right pan was replaced with a glass slide with copper wire and some additional weight, to maintain the both side of pan. The weight to separate the mucoadhesive from buccal mucosa was recorded as mucoadhesive strength.

In-vitro

Various models were designed by researchers to study the in-vitro release studies of the formulations based on the route of administration.

Some of the models are J.P. IX disintegration tester unaccompanied by the disc, Toyamo -Sangyo TR-553 dissolution tester, an apparatus close to that of insulin dosage form evaluation, along with a water jacket to control the temperature etc. The methods used are summarized in Table 1.

Research work on Mucoadhesive dosage forms

Numerous research works have been done on mucoadhesive drug delivery systems in the last two decades for various drugs in different routes of administration. The main objectives of this is to retain the dosage form at the required site to make a close contact of the dosage form with biological membrane to prolong the drug action. Even though the oral route is the most common, it is not suitable for drugs which produce gastrointestinal side effects and those are capable of gut and/or hepatic metabolism. Therefore, these dosage forms were developed with other routes of drug administration like ocular, nasal, buccal, vaginal and rectal routes to overcome the problems of oral administration. The duration of action and bioavailability of drugs were increased when we administered through these other routes.

CONCLUSION

Some of the mucoadhesive drug delivery systems, which are available in the market include Aftach tablet (Triamcinolone acetonide), Buccostem tablet (Prochlorperazine maleate), Rhinocort powder spray (Beclomethazonedipropionate), Salcoat...
powder spray (Beclomethasonedipropionate), Sucralfate (Aluminum hydroxide), and Susadrin tablet (Nitroglycerin). Even though there are very few mucoadhesive formulations available in the market currently, it may be concluded that these mucoadhesive formulations offers a great potential for both systemic and local use in the near future.

Conflict of Interest
None.

Funding Support
None.

REFERENCES


