IJPSR (2012), Vol. 3, Issue 08 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 April, 2012; received in revised form 14 May, 2012; accepted 17 July, 2012

NOVEL PARADIGMS IN MUCOADHESIVE DRUG DELIVERY SYSTEM

Deepak Sharma*, Mankaran Singh, Dinesh Kumar and Gurmeet Singh

CT Institute of Pharmaceutical Sciences, Shahpur, P.O- Udopur, Near Lambra, Jalandhar -144020, Punjab, India

Keywords:
Mucoadhesion,
Mucoadhesive Delivery System,
Mucoadhesive Polymers

Correspondence to Author:

Deepak Sharma

Street no 8, Mansa Devi Nagar, Phagwara, District- Kapurthala, Pin code: 144402, Punjab, India

Email: deepakpharmacist89@yahoo.com

ABSTRACT

Mucoadhesion is a field of current interest in the design of drug delivery systems. Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Mucoadhesive drug delivery system may be designed to enable prolonged residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface. Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving bioavailability. Application of these dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass metabolism. The present review describes mucoadhesion, mucoadhesive polymers and use of these polymers in designing different types of mucoadhesive gastrointestinal, nasal, ocular, vaginal and rectal drug delivery systems. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery.

INTRODUCTION: For the systemic delivery of drugs via various pharmaceutical product of different dosage form, the oral route drug delivery has been known as the most widely utilized route of administration among all other routes [1].

Thus, oral controlled dosage forms have been developed for the past three decades, due to their considerable therapeutic advantages. However, this approach has not been suitable for those drugs which are absorbed only in a particular portion of gastrointestinal tract (GIT) or which are absorbed in various segment of the GIT to a different extent. Such drugs are characterized by a narrow absorption window due to the relatively short transit time of the gastrointestinal tract i.e. stomach and small intestine [2]. Thus, after only a short period of less than 6 h, the CR-DF has already left the upper gastrointestinal tract and the drug is released in nonabsorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability [3]. Thus, the concept of mucosal adhesive or mucoadhesive was introduced in the early 1980's, into the field of control drug delivery.

Mucoadhesive drug delivery system are those delivery systems which utilizes the assets of bioadhesion of certain water –soluble polymer which on hydration become adhesive, thus can be used for targeting a drug or drug delivery system in particular region of the body for the extended period of time, not only for local targeting of drug but also for the better control of

systemic drug delivery [4]. It prolongs the residence time of the dosage form at the site of application or absorption and facilitates an intimate contact of the dosage form with the underline absorption surface and thus contributes to improved and/or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, gastrointestinal, rectal and vaginal routes for both systemic and local effects [2].

Bioadhesion is an interfacial phenomena in which two material, at least one of which being of a biological nature, are held together for an extended period of time by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane [5]. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface [6].

In biological systems, four types of bioadhesion could be distinguished;

1. Adhesion of a normal cell on another normal cell.
2. Adhesion of a cell with a foreign substance.
3. Adhesion of a normal cell to a pathological cell.
4. Adhesion of an adhesive to a biological substance [6, 7].

For the purpose of drug delivery, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. The phenomenon is referred to as mucoadhesion, if adhesive attachment is to a mucus coat. Bioadhesion can be modeled after a bacterial attachment to tissue surfaces, and mucoadhesion can be modeled after the adherence of mucus on epithelial tissue [8]. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye. The mucoadhesive drug delivery system may include the following [7];

- Gastrointestinal delivery system.
- Sublingual delivery system.
- Vaginal delivery system.
- Nasal delivery system.
- Ocular delivery system.
- Rectal delivery system.
- Buccal delivery system.

1. Need of Mucoadhesive Drug Delivery System [27]:

- Controlled release.
- Target & localized drug delivery.
- By pass first pass metabolism.
- Avoidance of drug degradation.
- Prolonged effect.
- High drug flux through the absorbing tissue.
- Reduction in fluctuation of steady state plasma level.

2. Advantages of Mucoadhesive Drug Delivery Systems [9]:

- A prolonged residence time at the site of drug action or absorption.
- A localization of drug action of the delivery system at a given target site.
- An increase in the drug concentration gradient due to the intense contact of particle with the mucosal.
- A direct contact with intestinal cells that is the first step before particle absorption.
- Ease of administration.
- Termination of therapy is easy.{except gastrointestinal}
- Permits localization of drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients. {except gastrointestinal}

- Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, there by offering a greater bioavailability.
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route. E.g. Buccal sublingual, vaginal.
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Systemic absorption is rapid.
- This route provides an alternative for the administration of various hormones, narcotic, analgesic, steroids, enzymes, cardiovascular agents etc.
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
- Less 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.
- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.

3. **The Mucus Layer** [7, 10]: The tissue layer responsible for the formation of the adhesive interface is mucus.

   Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini.

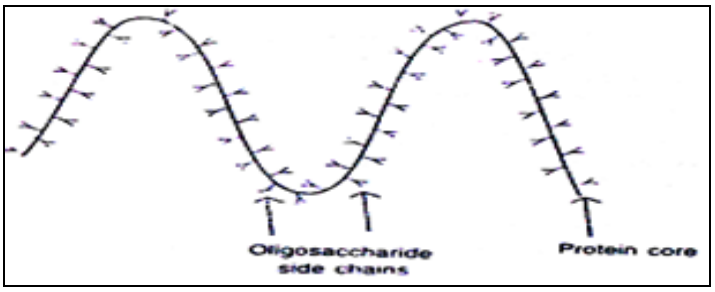
   The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathophysiological state. However, it has the following general composition.

TABLE 1: COMPOSITION OF MUCOUS MEMBRANE [52]

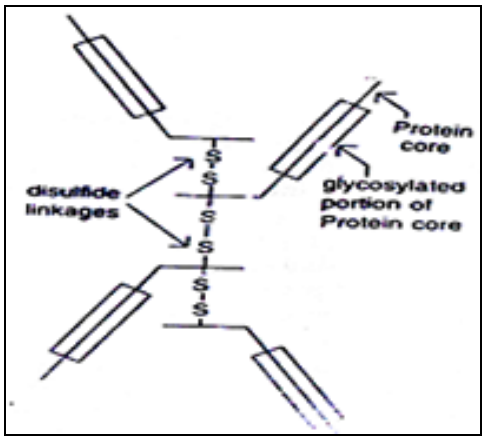
Components	Percentage
Water	95.00%
Glycoproteins and Lipids	0.5-5.0%
Mineral salts	0.5-1.0%
Free Proteins	0.5-1.0%

4. **Function of mucus layer [7]:** The primary functions of the mucus layer are:

   - **Protective:** Resulting particularly from its hydrophobicity and protecting the mucosa from the diffusion of hydrochloric acid from the lumen to the epithelial surface.
   - **Barrier:** The role mucus layer as barrier in tissue absorption of drugs and other substances is well known as it influences the bioavailibity of the drugs.
   - **Adhesion:** Mucus has strong cohesional properties and firmly binds to the epithelial cells surface as continuous gel layer.
   - **Lubrication: -** An important role of the mucus layer is to keep the mucosal membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.



A. GLYCOPROTEIN CHAIN



B. GLYCOPROTEIN TETRAMER

FIG. 1: SCHEMATIC REPRESENTATION OF MUCUS [3]

5. **Stages of Mucoadhesion:** The stages of mucoadhesion are generally divided in two steps:

I. Contact stage

II. Consolidation stage

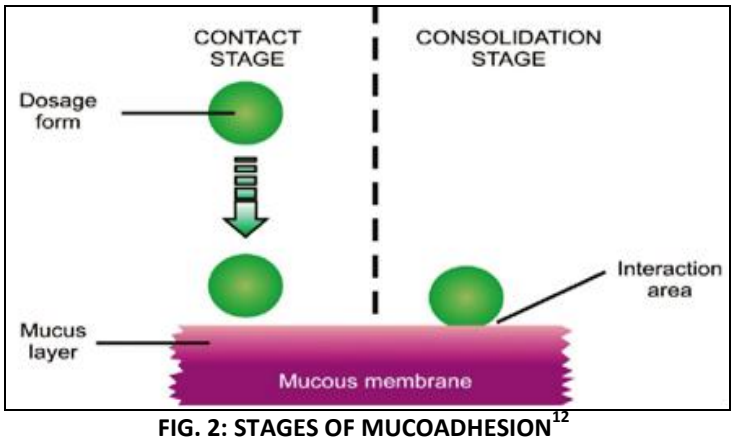


FIG. 2: STAGES OF MUCOADHESION[12]

The contact stage (**fig. 2**) 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. 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 [11].

In the consolidation step (fig. 2), 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 Vander Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step:

1) Diffusion theory

2) 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. For this to take place the mucoadhesive device has features favoring both chemical and mechanical interactions.

According to dehydration theory (**fig. 3**), 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 formulation or highly hydrated form [12].

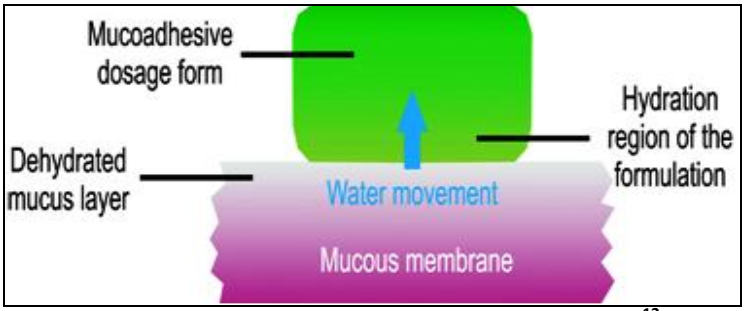


FIG. 3: DEHYDRATION THEORY OF MUCOADHESION [12]

6. **Mechanism of Mucoadhesion:** The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process:-

Step 1: Wetting and swelling of polymer

Step 2: Interpenetration between the polymer chains and the mucosal membrane.

Step 3: Formation of Chemical bonds between the entangled chains**.**

Step 1: In this step (**fig. 4**), when the polymer spreads over the surface of biological substrate or mucosal membrane, the wetting and swelling step occurs in order to develop an intimate contact with the substrate [11, 13]. By the help of the surface tension and forces that exist at the site of adsorption or contact, bioadhesives are able to adhere to or bond with biological tissues. Swellings of polymers occur because the components within the polymers have an affinity for water [14].

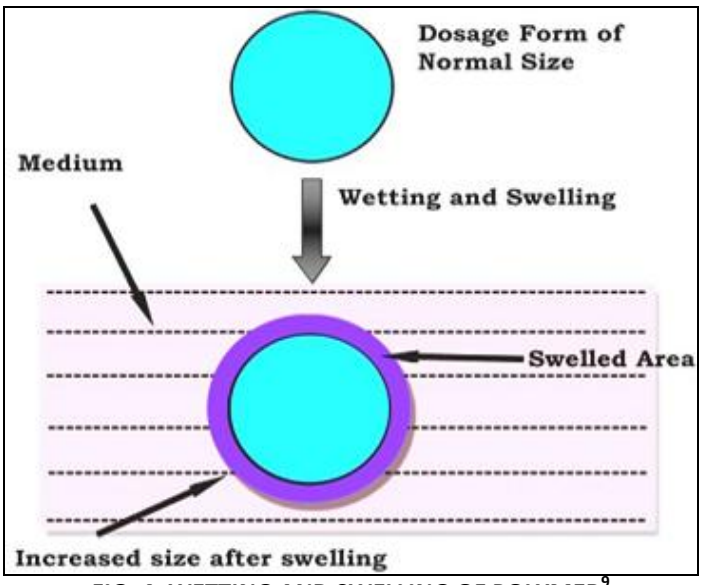


FIG. 4: WETTING AND SWELLING OF POLYMER[9]

Step 2: The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In this step (**fig. 5**) inter-diffusion and inter-penetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact [11, 15]. The strength of this bond depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure [14, 16].

Step 3*:* In this step (**fig. 6**), entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule [11, 14]. The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as Vander Waals interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bioadhesive formulations in which strong adhesions between polymers are formed [11].

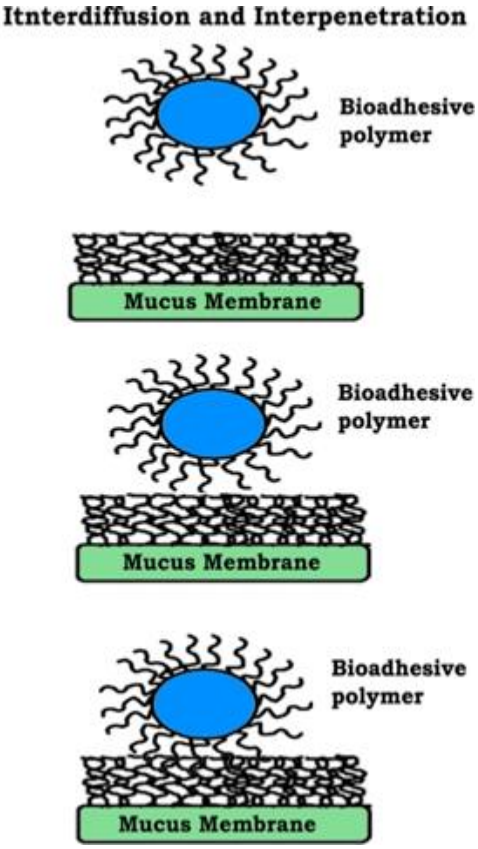


FIG. 5: INTERDIFFUSION AND INTERPENETRATION OF POLYMER AND MUCUS [9]

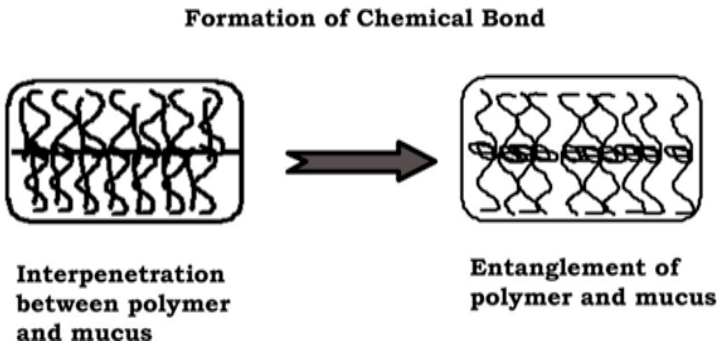


FIG. 6: ENTANGLEMENT OF POLYMER AND MUCUS BY CHEMICAL BONDS [9]

Theories of Mucoadhesion:

1. **The Wettability Theory:** The wettability theory is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the ''spreadability" of the API delivery system across the biological substrate. This theory postulates that the adhesive component penetrates surface irregularities, hardens and anchors itself to the surface. The adhesive performance of such elastoviscous liquids may be defined using wettability and spreadability; critical parameters that can be determined from solid surface contact angle measurements. This process defines the energy required to counter the surface tension at the interface between the two materials allowing for a good mucoadhesive spreading and coverage of the biological substrate [17].

   The wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant. The work of adhesion [expressed in terms of surface and interfacial tension (Y) being defined as energy per cm^2 released when an interface is formed. According to Dupres equation work of adhesion is given by;

$$Wa = Y_A + Y_B - Y_{AB}$$

Where, A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$Wc = 2Y_A \text{ or } Y_B$$

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane [18].

Mucoadhesive polymer systems that exhibit similar structure and functional groupings to the mucus layer will show increased miscibility; this in turn will result in a greater degree of polymer spreadability across the mucosal surface. Lower water: polymer contact angles of such systems will facilitate hydration of the polymer chains and thus promote intimate contact between polymeric delivery platform and the mucus substrate. In the case of an extremely hydrophilic polymer however, the water contact angle will be much lower than that of the mucosal surface, thus discouraging such an intimate contact due to a high interfacial surface free energy [19].

2. **The Electronic Theory:** According to this theory adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer [20].

3. **The Adsorption Theory:** According to adsorption theory, the material adheres after an initial contact between two surfaces because of surface forces acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces are:

   Primary Bonding- It occurs mainly due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency [21].

   Secondary Bonding- It mainly arise due to Vander Waals interactions, hydrogen bonds, electrostatic attraction, hydrophobic interactions, these interactions require less energy to 'break' they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds [22].

4. **The Diffusion-Interlocking Theory:** This theory (**fig. 7**) proposes the time-dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer. This is a two-way diffusion process with penetration rate being dependent upon the diffusion coefficients of both interacting polymers. Although there are many factors involved in such processes, the fundamental properties that significantly influence this inter-movement are

molecular weight, cross-linking density, chain mobility/flexibility and expansion capacity of both networks [18]. Furthermore, temperature also has been noted as important environmental factor for this process [23].

Whilst it is acknowledged that longer polymer chains may diffuse, interpenetrate and ultimately entangle to a greater extent with surface mucus, it should be recognized that a critical chain length of at least 100,000 Da is necessary to obtain interpenetration and molecular entanglement. Additionally excessive chain cross-linking will act to decrease the polymer mobility and thus interfacial penetration [24].

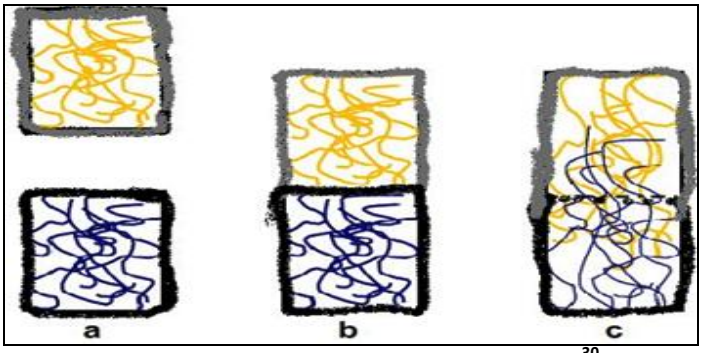


FIG. 7: DIFFUSION- INTERLOCKING THEORY [30]

The diffusion- interlocking theory of adhesion:

a. Top (polymer) layer and bottom (mucus) layer before contact
b. Top layer and bottom layer immediately after contact.
c. Top layer and bottom layer after contact for a period of time.

5. **The Fracture Theory:** The fracture theory analyzes the force that is required for the separation of two surfaces after adhesion. It is considered to be appropriate for the calculation of fracture strengths of the adhesive bonds involving rigid mucoadhesive materials [25] and has frequently been applied to the analysis of tensile strength measurements on, for example, microspheres and powder specimens [26]. The maximum tensile strength produced during detachment can be determined by dividing the maximum force of detachment (F) by the total surface area (A) involved in the adhesion interactions. The equation can be written as:

$$S_m = F_m / A_m$$

These general theories are not particularly useful in establishing a mechanistic base to bioadhesives, but they do identify the variables that are important to the bioadhesion process [18].

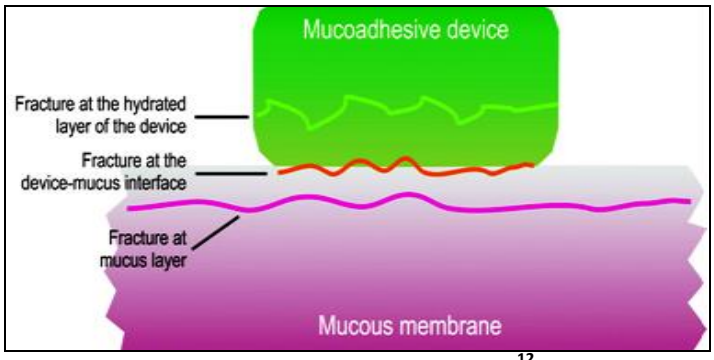


FIG. 8: THE FRACTURE THEORY[12]

TABLE 2: DIFFERENT THEORIES EXPLAINING THE MECHANISM OF MUCOADHESION [59]

Theory	Mechanism of Mucoadhesion	Comments
Wetting Theory	Ability of bioadhesive material to spread and develop intimate contact with the mucus membranes.	Spreading coefficient of polymer must be positive and contact angle between the polymer and the cells must be near to zero.
Electronic Theory	Attractive electrostatic forces between glycoproteins mucin network and the bioadhesive material.	Electron transfer occurs between the two forming a double layer of electrical charge at the interface.
Adsorption Theory	Surface forces resulting in the semi-permanent physical/ chemical bonding.	Strong primary forces: covalent bonds Weak secondary forces: ionic bonds, hydrogen bonds and Vander Waals forces
Diffusion Theory	Physical entanglement of mucin strands at the flexible polymer chain and interpenetration of mucin strands into the porous structure of the polymer substrate.	For maximum diffusion and the best bioadhesive strength: solubility parameters of the bioadhesive material and the mucus glycoproteins must be similar.
Fracture Theory	Analyses the maximum tensile strength developed during detachment of bioadhesive drug delivery systems from the mucosal surface.	Does not require the physical entanglement of the bioadhesive polymer chains and mucin strands, hence appropriate to study the bioadhesion of hard polymers which lacks the flexible chains.

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

Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

All three polymer types can be used for drug delivery [28].

Ideal Muco Polymer Characteristics: A mucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva. As understood earlier, that various physical and chemical exchanges can affect the polymer/mucus adhesion, so as polymer should be carefully selected with the following properties in mind [29].

1. Polymer must have a high molecular weight up to 100.00 or more this is necessary to promote the adhesiveness between the polymer and mucus [29].
2. Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem [30].
3. High viscosity.
4. Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly cross linked polymers swell in presence of water and retain their structure. Swelling favors controlled release of the drug and increases the polymer/mucus interpenetration. But as the cross linking increases, the chain mobility decreases which reduces the mucoadhesive strength [30].
5. Spatial conformation.
6. Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network [31].
7. Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form. For solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi solid dosage forms an optimum concentration essential beyond which the adhesive strength decreases [32].
8. Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage [33, 34, 35].
9. Optimum pH – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making them more available for interdiffusion and interpenetration [36]. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces [18].
10. High applied strength and initial contact time
11. It should non toxic, economic, biocompatible preferably biodegradable [37].

1. **Classification of Mucoadhesive Polymer:** The rheology of the mucoadhesion is a typical topic and it deals with a number of forces, factors of the components, state of the material, its derived properties. Based on the rheological aspects, we can categorize the mucoadhesive polymers into

two broad categories, materials which undergo matrix formation or hydrogel formation by either a water swellable material or a water soluble material. These carriers generally polymers are classified as;

a. Hydrophilic polymers

b. Hydrogels

a. **Hydrophilic Polymers:** The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers [24]. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose, have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer [38, 39].

Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties [40]. Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property [24]. The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. In a recent study, partially neutralized poly (acrylic acid) complex was developed in the presence of levobetaxolol hydrochloride, a potent cardiac β-blocker.

The delivery system was prone to dissolution as the time progressed due to the release of the incorporated drug [41]. Mucoadhesive microcapsules can be designed with same principle by using orifice-ionic gelation method. This technique has been used to design a delivery system of gliclazide, an anti-diabetic drug, using sodium alginate, sodium carboxymethyl cellulose, carbopol 934P and hydroxy propylmethyl cellulose. The delivery system showed the release of gliclazide for an extended period of time due to its mucoadhesive properties [42]. The hydrophilic polymers form viscous solutions when dissolved in water and hence may also be used as viscosity modifying/enhancing agents in the development of liquid ocular delivery systems so as to increase the bioavailability of the active agents by reducing the drainage of the administered formulations [24, 43].

These polymers may be directly compressed in the presence of drugs so as to have a mucoadhesive delivery system [44]. Numerous polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan gum, gellan gum, guar gum, and carrageenan have found applications in ocular mucoadhesive delivery systems [24]. Cellulose and its derivates have been reported to have surface active property in addition to its film forming capability [40, 45].

Cellulose derivatives with lower surface acting property are generally preferred in ocular delivery systems as they cause reduced eye irritation. Of the various cellulose derivates, sodium carboxymethyl cellulose has been found to have excellent ocular mucoadhesive property. Cationic cellulose derivatives (e.g. cationic hydroxyethyl celluloses) have been used in conjunction with various anionic polymers for the development of sustained delivery systems [24, 46].

b. **Hydrogels:** Hydrogels can be defined as three-dimensionally crosslinked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. In general, with the increase in the crosslinking density there is an associated decrease in the mucoadhesion. Thielmann *et al.,* reported the thermal crosslinking of poly (acrylic acid) and methyl cellulose. They reported that with the increase in the crosslinking density, there was a reduction in the solubility parameters and swelling which resulted in a reduction of mucoadhesion [47]. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property with the increase in the crosslinking density and was attributed to increase in the poly (acrylic acid)

chain density per unit area [48]. Acrylates have been used to develop mucoadhesive delivery systems which have the ability to deliver peptide bioactive agents to the upper small intestine region without any change in the bioactivity of the peptides. In a typical experimentation, Wood and Peppas developed a system in which ethylene glycol chains were grafted on methacrylic acid hydrogels and were subsequently functionalized with wheat germ agglutinin.

Wheat germ agglutinin helped in improving the intestinal residence time of the delivery system by binding with the specific carbohydrate moieties present in the intestinal mucosa [49]. In addition to the drug targeting, mucoadhesive hydrogel based formulations for improving the bioavailability of the poorly water soluble drug. Muller and Jacobs prepared a nanosuspension of buparvaquone, a poorly water soluble drug, by incorporating it within carbopol and chitosan based hydrogels. The mucoadhesive delivery systems showed improved bioavailability of the drug when compared over the nanosuspension. This was attributed to the increased retention time of the delivery system within the gastrointestinal tract [50].

Newer Second Generation Polymers [51]: They have the following advantages:

- More site specific hence called cytoadhesives.
- Are least effected by mucus turnover rates.
- Site specific drug delivery is possible.

a) **Lectins- mediated Bioadhesive Polymers**: Specific proteins or glycoproteins, such as lectins, which are able to bind certain sugars on the cell membrane, can increase bioadhesion and potentially improve drug delivery via specific binding and increase the residence time of the dosage form. This type of bioadhesion should be more appropriately termed as cytoadhesion. A site-specific interaction with the receptor could potentially trigger intercellular signaling for internalization of the drug or the carrier system (endocytosis through cytoadhesion) into the lysosomes or into other cellular compartments, such as the nucleus (Figure 8). The recent idea of developing blectinomimetics (lectin-like molecules) based on lectins, and even biotechnologically generated derivatives of such molecules, holds an interesting future for this class of bioadhesion molecules [52].

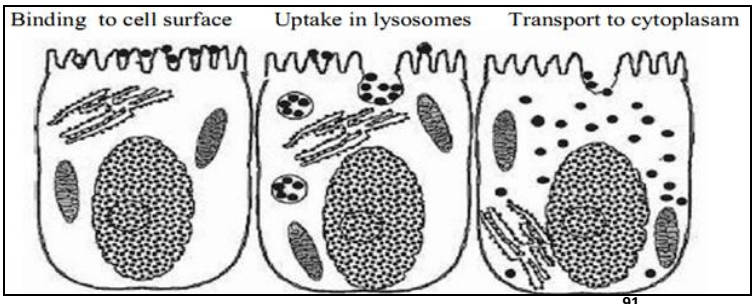


FIG. 9: LECTIN MEDIATED BIOADHESIVE SYSTEM [91]

b) **Thiolated Mucoadhesive Polymers**: These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gallan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from the delivery system due to increased rigidity and cross linking [53]. Improved mucoadhesive properties of the thiolated polymers:

- Improved tensile strength,
- High cohesive properties,
- Rapid swelling and water uptake behavior have made them an attractive new generation of bioadhesive polymers.

TABLE 3: DIFFERENT TYPE OF THIOMERS AND THE EFFECT ON MEASURED MUCOADHESION [54]

Polymer	Mucoadhesive bond strength
Chitosan- iminothiolane	250- fold improved mucoadhesive properties
Poly(acrylic acid)-cysteine	100- fold improved mucoadhesive properties
Poly(acrylic acid)-homocysteine	Approximately 20- fold improved mucoadhesive properties
Chitosan-thioglycolic acid	Ten fold improved mucoadhesive properties
Chitosan-thioethtlamidine	Nine fold improved mucoadhesive properties
Alginate -cysteine	Four fold improved mucoadhesive properties
Poly(methacrylic acid)-cysteine	Improved cohesive and mucoadhesive properties
Sodium carboxymethyllcellulose-cysteine	Improved mucoadhesive properties

c) Polyox WSRA: Class of high molecular weight polyethylene molecular weight polyethylene oxide. Homopolymers having the following properties [55],

- Water soluble
- Hydrophilic nature
- High molecular weight
- Functional group for hydrogen bonding
- Biocompatible and non toxic
- Can be formulated into tablets, films, gels, microcapsules, syrups.

d) **Bacterial Adhesion:** The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. The ability of bacteria to adhere to a specific target is rooted from particular cell-surface components or appendages, known as fimbriae that facilitate adhesion to other cells or inanimate surfaces. These are extracellular, long thread like protein polymers of bacteria that play a major role in many diseases.

Bacterial fimbriae adhere to the binding moiety of specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicity. The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins. Bernkop-Schnurch *et al*., covalently attached a fimbrial protein (antigen K99 from *E. coli*) to poly (acrylic acid) polymer and substantially improved the adhesion of the drug delivery system to the GI epithelium using a system as depicted [56].

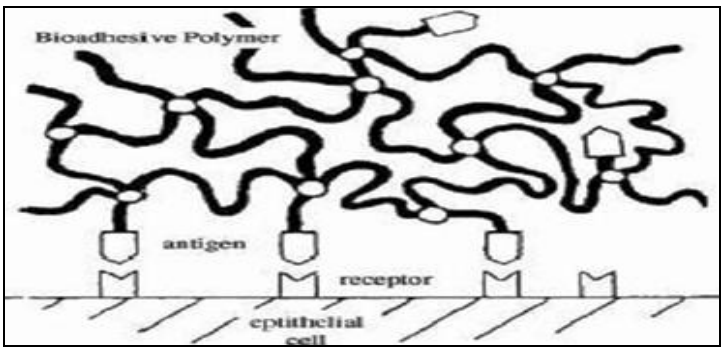


FIG. 10: BACTERIAL ADHESION -A DIAGRAM OF COVALENTLY ATTACHED FIMBRIAL PROTEIN (K99 FROM E. COLI) TOPOLY (ACRYLIC ACID) AS A CARRIER SYSTEM [91]

Factors Affecting Mucoadhesion:

1. **Polymer-Related Factors:**

a. **Molecular Weight of the Polymer:** The optimum molecular weight for maximum mucoadhesion depends upon the type of mucoadhesive polymer and tissue. With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer. In general, polymers having MW ≥ 100,000 have been found to have adequate mucoadhesive property for biomedical applications. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has enhanced, and a PEG with 400,000 has superior adhesive properties [57, 58]. Interpretation is more critical for lower molecular weight polymers to be an excellent bioadhesive, whereas Entanglement is important for higher molecular weight polymers [59].

b. **Concentration of Active Polymers:** There is an optimum concentration of polymer corresponding to the best bioadhesion. In extremely concentrated systems, beyond the optimum level, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited [3]. 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 [11].

c. **Flexibility of Polymer Chains:** It is critical for interpenetration and entanglement. Mobility of individual polymer chains decrease as water-soluble polymers become crosslinked and thus the valuable length of the chain that can penetrate into the mucus layer decreases, which reduces mucoadhesive strength [60].

d. **Spatial Conformation:** Despite a high molecular weight of 19,500,000 for dextrans, spatial conformation of a molecule is also important. They have adhesive strength similar to that of polyethylene glycol, which has a molecular weight of 200,000. The helical conformation of electrons may shield many adhesively active groups, primarily responsible for adhesion unlike PEG

polymers that have a linear conformation. Also the effect of polymer concentration is dependable on the physical state (solid / liquid) of the bioadhesive drug delivery systems; more is the polymer concentration results the higher bioadhesive strength in Solid BDDS while an optimum concentration is required for best bioadhesion in liquids [61].

e. **Swelling (Hydration):** Swelling characteristics are related to the mucoadhesive itself and its environment. Swelling depends on the polymer concentration, the ionic strength, and the presence of water. During the dynamic process of bioadhesion, maximum bioadhesion in vitro occurs with optimum water content. Over hydration results in the formation of a wet slippery mucilage without adhesion [3].

2. **Environment Related Factors:**

a. **Applied Strength:** To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesive strength increases with the applied strength or with the density of its application up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a satisfactory longer period of time polymers become mucoadhesive even though they do not have attractive interaction with mucin [28, 62].

b. **pH at Polymer Substrate Interface:** pH can influence the formal charge on the surface of the mucus as well as certain ionizable mucoadhesive polymers [57]. Mucus will have a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone [3, 63].

Some studies had shown that the pH of the medium is important for the degree of hydration of cross-linked polycyclic acid, showing consistently increased hydration from pH 4 through pH 7, and then a decrease as alkalinity or ionic strength increases, for example polycarbophil does not show a strong mucoadhesive property above pH 5 because uncharged, rather than ionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However, at higher pH, the chain is fully extended due to electrostatic repulsion of the carboxylate anions [3, 57, 28, 64].

c. **Initial Contact Time:** Contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. More mucoadhesive strength increases as the initial contact time increases [60].

3. **Physiological Variables:**

a. **Mucin Turnover:** The natural turnover of mucin molecules from the mucus layer is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter how high the mucoadhesive strength is. Mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesive.

Second, mucin turnover results in substantial amount of soluble mucin molecules. These molecules interact with mucoadhesives before they have a chance to interact with mucus layer [65, 66, 67]. Mucin turnover may depend on the other factors such as presence of blood. Lehr et al. (1991) calculated mucin turnover time of 47-270 minutes [65]. The ciliated cells in the nasal cavity are known to transport the mucus to the throat at a rate of 5mm/min. the mucociliary clearance in the tracheal region has been found to be in the range of 4-10mm/min [28, 63, 66, 67].

b. **Disease States:** Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If mucoadhesives are to be used in the diseased state, the mucoadhesive property needs to be evaluated under it [68, 69, 70].

Potential sites for Mucosal Drug Delivery: 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 [71].The use of mucoadhesive formulations has been widely exploited for their targeted and controlled release delivery to many mucosal membrane-based organelles. Such formulations may deliver API for local or systemic effect, while bioavailability limiting effects such as enzymatic or hepatic degradation can be avoided or minimized [72]. 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 [71].

1. **Gastrointestinal Drug Delivery System:** Mucoadhesive polymers may offer increased intimacy with the lining of the GI tract and hence bioavailability. Furthermore, ‘‘absorption windows” within the GI tract such as those making up the gastro-associated lymphatic tissue may be targeted allowing for the absorption of larger poorly soluble therapeutic agents [73].

   Therefore, a primary objective of using mucoadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once-daily dosing. A number of mucoadhesive-based dosage forms, including sustained-release tablets, semisolid forms, powders, and micro- and/or nanoparticles in the GI tract, have been widely studied. Nonetheless, successful systems that will be retained in the GI tract of humans for a desirable time have not yet been developed [74, 66].

   Matharu and Sanghavi used carbopol 934P and poly (acrylic acid) cross-linked with 0.001% ethylene glycol to prepare mucoadhesive tablets for captopril [75]. Second-generation vehicles are now receiving increased attention. A thiolated chitosan tablet has recently been reported for the oral delivery of insulin. Further advances in this field have included the attachment of second-generation mucoadhesives to the surface of microspheres [76].

2. **Buccal Drug Delivery System:** The buccal cavity offers many advantages for drug delivery application, the most pertinent being high accessibility and low enzymatic activity. Additionally, buccal drug delivery can be promptly terminated in cases of toxicity through the removal of dosage form thereby offering a safe and easy method of drug utilization [77].

   First-generation mucoadhesives, such as sodium carboxy methylcellulose, hydroxypropylcellulose examined for the treatment of periodontal disease and the controlled delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides [78]. Although gel and ointments are the most patient convenient; tablets, patches and films have also been examined. Drug delivery to accessible cutaneous sites such as the buccal cavity is often associated with high patient compliance, low levels of irritation and offers significant ease of administration. Other less reported advantages include rapid onset of action due to a highly vascularised buccal mucosa and avoidance of hepatic first-pass metabolism [79].

3. **Nasal Drug Delivery System:** Nasal delivery has been obtained using solutions, powders, gels and microparticles. The nasal epitheliums have relatively high permeability, two cell layers separating the nasal lumen from the dense vasculature within the lamina propria. The most commonly employed intranasal APIs are solutions containing sympathomimetic vasoconstrictors for immediate relief of nasal congestion. Local delivery of these alpha adrenergic stimulators is of particular benefit to patients with high blood pressure (or those at heightened risk of cardiovascular incident), as vasoconstriction will occur to the greatest degree within the nose. In addition to local effects, intranasal route of drug administration has also been used to achieve a distal systemic effect [80].

   One of the key advantages provided by intranasal drug delivery is that the nasal cavity provides a large highly vascularised surface area through which first pass metabolism can be avoided, as blood is drained directly from the nose into the

systemic circulation [81]. Polymeric components such as hydroxylpropylcellulose, chitosan, carbomer, NaCMC, hyaluronic acid and polyacrylic acid have all shown promise as mucoadhesive agents for use in controlled drug delivery to pulmonary and nasal sites. Such polymeric delivery platforms may be used either alone or as synergistic combination systems [82]. One of the most interesting areas of research within this field has been the use of intranasal drug delivery for the induction of antibody responses in serum, as well as local and distal mucosal secretions, due to absorption through the nasal-associated lymphoid tissue (NALT) [83].

4. **Ocular Drug Delivery System:** The delivery of therapeutic agents to the eye may be achieved using various types of dosage forms including liquid drops, gels, ointments and solid ocular inserts (both degradable and non-degradable) [79, 84]. Another interesting delivery system is in situ gelling polymer that undergoes a phase transition after application. Pre-application these systems are in the liquid state and are easily administered, whereas post-application they are transformed in highly viscous networks.

   Mucoadhesive polymers would be expected only to attach to conjunctival mucus in vivo, but migration may result in causing deposition of semisolid within the corneal area, bringing with it a detrimental effect on visual acuity [86]. Additionally limited bio-availability has been experienced in vivo for carbomer and polycarbophil as a result of the high swelling capacity of such polymers in the neutral pH environment of the eye. Maintenance of a low viscosity in such systems through pH regulation in the range 4–5 is not acceptable as it may result in patient unease and mild lacrimation, both of which will have an effect on treatment success [87].

5. **Vaginal Drug Delivery System:** Recently, vaginal mucoadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases. For drugs that are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal delivery may offer a number of advantages over the other routes of administration. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for extended periods of time including daytime and nighttime, thereby enabling lower dosing frequencies. The vagina is a fibromuscular tube connecting the uterus to the exterior of the body. The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface.

   Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid. In general, traditional vaginal dosage forms include solutions, suspensions, gels, microparticles, suppositories, creams, foams, and tablets and all have a relatively short contact time. Robinson et al. reported on a system of treatment using a gel containing the mucoadhesive polycarbophil that remained on vaginal tissue for 3-4 days and hence served as a platform for delivery of drug such as progesterone [71].

6. **Rectal Drug Delivery System:** It is another way to deliver the drug by using mucoadhesive polymers is through the mucous membrane of the rectum. Hydrogels administered rectally have proven to be useful for drug delivery [71]. Leede *et al*., proposed that hydrogels using hydroxy ethyl methacrylate cross-linked with ethylene glycol dimethacrylate and including antipyrine and theophyiline as model drugs provided rate-controlled drug delivery [88].

Techniques to evaluate Mucoadhesion [89]:

1. ***In vitro* methods:**

   - Tensile strength measurement.
   - Shear strength measurement.
   - Modified physical balance.
   - Detachment force method.
   - Microbalance method.
   - Ex-vivo mucoadhesion.
   - Falling film method.

- Swelling index.
- Wash off method.
- Colloidal gold staining.
- Adhesion number.
- Viscometric method.
- Everted sac technique.
- Drug permeation.
- Fluorescent probe method.
- Mucoadhesion time.
- Surface pH study.
- Scanning Electron microscopy. (SEM)
- Novel Rheological Approach.
- Texture analyzer.

2. ***In vivo* methods:**
    - Use of radioisotopes.
    - Use of gamma scintigraphy.
    - X-ray studies
    - In vivo evaluation of mucoadhesive studies
    - Isolated loop technique.
3. ***In vitro* as well as *in vivo* method:**
    - Biacore (Surface Plasmon Resonance)

CONCLUSION: Mucoadhesive drug delivery systems have a high potential of being useful means of delivering drugs to the body, perhaps particularly for topical or local administration where the mechanical trauma experienced by the dosage form may be minimized.

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. Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. 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 great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals. The mucoadhesive drug delivery system will continue to appeal to both pharmaceutical researchers and the pharmaceutical industry.

ACKNOWLEGDEMENT: Authors are highly acknowledged to Dr. Mahendra Singh Rathore from CT Institute of Pharmaceutical Sciences, Jalandhar for his valuable suggestions, necessary help, and support and to the Library Department of Pharmaceutical Sciences of institute, for providing literature facilities for preparation of this review article.

REFERENCES:

1. Smart, John D. The basics and underlying mechanisms of mucoadhesion. Adv. Drug Del. Rev. 2005; 57(11): 1556-1568.
2. Bhatt DA, Pethe AM, Mucoadhesive Drug Delivery Systems: An Overview. J. Pharm. Res. 2010; 3(8):1743-1747.
3. Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP, Rajgor NB. Stomach specific mucoadhesive tablets as controlled drug delivery system - A Review work. Int. J. Pharm. Bio. Res. 2010; 1(1): 30-41.
4. Webster's Encyclopedic Unabridged Dictionary of the English Language. Thunder Bay Press, Avenel (NJ, USA), 2001.
5. Bibin KD, Deepa P**.** Mucoadhesive Agents, B.Pharm. Project and review articles. 2009; 1: 1-29.
6. Castellanous J. Mucoadhesive drug delivery systems. J. Pharm. 1993; 12: 246.
7. Jain NK. Controlled release and Novel Drug Delivery. 1st ed. CBS publishers and Distributors New Delhi; 1997. p. 353-370.
8. Longer MA, Robinson JR. Fundamental Aspects of Bioadhesion. Pharm. Int. 1986; 7: 114-117.
9. Alexander A, Ajazuddin, Tripathi DK, Verma T, Swarna, Maurya J, Patel S. Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system: A review. Int. J. Appl. Bio. Pharm. Tech. 2011; 2(1): 434-441.
10. Park H, Robinson JR. Mechanisms of mucoadhesion og polyacrylic acid and hydrogels. Pharm. Res.1987; 4: 457-464.
11. Hagerstrom H. Polymer gels as pharmaceutical dosage forms: rheological performance and physicochemical interactions at the gel-mucus interface for formulations intended for mucosal drug delivery. Uppsala. 2003; 76.

12. Flavia CC, Marcos LB, Raul CE, Maria Palmira Daflon Gremião. Mucoadhesive drug delivery systems. Brazilian J. Pharm. Sci. 2010; 46(1): l-17
13. Bhatt JH. Designing and evaluation of mucoadhesive microspheres of metronidazole for oral controlled drug delivery. Pharmainfo.net. 2009; 2: 1-13.
14. Sheila A. Bioadhesive Polymers, Power Point Presentation, Slide No.1-50.userweb.port.ac.uk/~roldom/Mucoadhesives/Bioadhesives.ppt.
15. Sharma HK, Sarangi B, Pradhan, Prasad S. Preparation and in-vitro evaluation of mucoadhesive microbeads containing Timolol Maleate using mucoadhesive substances of *Dillenia indica L.* Arch. Pharm. Sci. Res. 2009; 1: 181 -188.
16. Smart, JD. The basics and underlying mechanisms of mucoadhesion. Sci. Dir. 2005; 57(11): 1556-1568.
17. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Adv. Drug Del. Rev. 2005; 57: 1640–1665.
18. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: The next generation. J Pharm. Sci. 2000; 89(17): 850-866.
19. Shojaei A, Li X. Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethylether monomethacrylate. J. Control Rel. 1997; 47: 151–161.
20. Dodou D, Breedveld P, Wieringa P. Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel application. Eur. J. Pharm. Biopharm. 2005; 60: 1–16.
21. Kinloch AJ. The science of adhesion. J. Mater. Sci. 1980; 1: 2141–2166.
22. Castellanos MRJ, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 1993; 19: 143–194.
23. Jabbari E, Peppas NA. A model for inter diffusion at interfaces of polymers with dissimilar physical properties. Polymer. 1995; 36(3): 575–586.
24. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv. Drug Del. Rev. 2005; 57: 1595–1639.
25. Chickering-III DE, Mathiowitz E. Fundamentals of bioadhesion. In Bioadhesive drug delivery systems-Fundamentals, Novel Approaches and Development. Mathiowitz E, Chickering-III DE, Lehr CM (eds.), Dekker M; 1999. p.1-85.
26. Bredenberg S, Nystrom C. In vitro evaluation of bioadhesion in particulate systems and possible improvement using interactive mixtures. J. Pharm. Pharmacol. 2003; 55: 169 - 177.
27. Abnawe SA. Mucoahesive Drug Delivery System, Pharmainfo.net. 2009.
28. Chowdary KPR, Shrinivasrao Y. Mucoadhesive drug delivery systems: A review of current status. Indian Drugs. 2000; 37 (9): 400- 406.
29. Allur HH, Johnston TP, Mitra AK, In; Swarbrick J, Boylan JC. Encyclopedia of Pharmaceutical Technology. Marcel Dekker, NewYork; 1990; 20(3).p. 193-218.
30. Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of Mucoadhesion and bioadhesion: tethered structures and site specific surfaces. J. Control Rel. 2000; 65: 63-71.
31. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery – A Promising option for orally less efficient drugs. J. Control Rel. 2006; 114 (1): 15-40.
32. Imam ME, Hornof M, Valenta C, Reznicek G, Bernkop SA. Evidence for the interpretation of mucoadhesive polymers into the mucus gel layer. STP Pharma. Sci. 2003; 13:171-176.
33. Bernkop SA, Freudl J. Comparative in vitro study of different chitosan- complexing agent conjugates. Die Pharmazie. 1999; 54(5): 369-371.
34. Hagerstrom H, Paulsson M, Edsman K. Evaluation of mucoadhesion for two Eur. polyethylene gels in simulated physiological condition using a rheological method. J. Pharm. Sci. 2000; 9(3): 301-309.
35. Sigurdsson H, Loftsson T, Lehr C. Assessment of mucoadhesion by a resonant mirror biosensor. Int. J. Pharm. 2006; 325(1-2): 75-81.
36. Mortazavi SA, Smart J. An investigation into the role of water movement and mucus gel dehydration in mucoadhesion. J. Control Rel. 1993; 25: 197-203.
37. Peppas N, Huang Y. Nanoscale technology of mucoadhesive interactions. Adv. Drug Deliv. Rev. 2004; 56 (11): 1675-1687.
38. Andrew GP, Laverty TP, Jones DS. Mucoadhesive polymeric for controlled drug delivery. Eur. J. Pharm. Biopharm. 2009; 71 (3): 505-518.
39. Rossi S, Bonferoni MC, Ferrari F, Caramella C. Drug release and washability of mucoadhesive gels based on sodium carboxymethylcellulose and polyacrylic acid. Pharm. Dev. Tech. 1999; 4 (1): 55-63.
40. Portero A, Osorio DT, Alonso MJ, Lopez CR. Development of chitosan sponges for buccal administration of insulin. Carbohydrate Polymers. 2007; 68 (4): 617-625.
41. Lele BS, Hoffman AS. Insoluble ionic complexes of polyacrylic acid with a cationic drug for use as a mucoadhesive, ophthalmic drug delivery system. J Biomater Sci. Polym. Ed. 2000; 11(12): 1319-1331.
42. Prajapati SK, Tripathi P, Ubaidulla U, Anand V. Design and Development of Gliclazide Mucoadhesive Microcapsules: In Vitro and In Vivo Evaluation. AAPS Pharm. Sci. Tech. 2008; 9 (1): 224-230.
43. Hui Hand Robinson J R. Ocular delivery of progesterone using a bioadhesive polymer. Int. J. Pharm. 1985; 26 (3): 203-213.
44. Juliano C, Gavini E, Cossu M, Bonferoni MC, Giunchedi P. Mucoadhesive alginate matrices containing sodium carboxymethyl starch for buccal delivery: In vitro and in vivo studies. J. Drug Del. Sci. Tech. 2004; 14 (2):159-163.
45. Benedetto DA, Shah DO, Kaufman HE. The instilled fluid dynamics and surface chemistry of polymers in the preocular tear film. Investigative Ophthalmology. 1975; 14 (12): 887-902.
46. Marlin L and Yamamoto R K. Muco-adhesive polymers. United States Patent 5358706. Available at: http://www. freepatentsonline. com/5358706.html
47. Thielmann F, Naderi M, Khutoryanskiy V, Khutoryanskaya O. Mucoadhesive hydrogel films based on blends of poly(acrylic acid) and methylcellulose. Available at: http://www.aapsj.org/abstracts/NBC_2007/NBC07-000679.PDF.
48. Warren SJ, Kellaway IW. The synthesis and in vitro characterization of the mucoadhesion and swelling of poly (acrylic acid) hydrogels. Pharm. Dev. Tech. 1998; 3(2):199-208.
49. Kristy MW, Peppas NA. Mucoadhesive Oral Insulin Delivery Systems Using Lectin Functionalized Complexation Hydrogels. Available at: http://aiche.confex.com/aiche/2005/preliminary program/abstract_31567.html
50. Muller RH, Jacobs C. Buparvaquone mucoadhesive nanosuspension: preparation, optimization and long-term stability. Int. J. Pharm. 2002; 237 (1-2): 151-161.
51. Andrews GP, Thomas P, Laverty TP, David S, Jones SD. Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharm. Biopharm. 2009; 71: 505-518.
52. Lehr CM. Lectin-mediated drug delivery: the second generation of bioadhesives. J. Control Rel. 2000; 65: 19– 29.
53. Berkop SA. Thiomers: a new generation of mucoadhesive polymers. Adv. Drug Del. Rev. 2005; 57: 1569- 1582.

54. Bernkop SA, Alexander HK, Verena M, Palmberger T: Thiomers. Eur. J. Pharm. Biopharm. 2004; 58(2), 253-263.
55. Lehr C. Lectin mediated drug delivery: the second generation of bioadhesives, J. Control Rel. 2000; 65: 135-143.
56. Schnurch AB, Gabor F, Szostak MP, Lubitz W. An adhesive drug delivery system based on K99-fimbriae. Eur. J. Pharm. Sci. 1995; 3: 293– 299.
57. Kumar RS, Bala P. Bioadhesive Polymeric Platforms for Transmucosal Drug Delivery Systems. Tropical J. Pharm. Res. 2010; 9: 91-104
58. Hoffman A. Pharmacodynamic aspects of sustained release preparations. Adv. Drug Del. Rev. 1998; 33:185-99.
59. Sachan NK, Bhattacharya A. Basics and Therapeutic Potential of Oral Mucoadhesive
Microparticulate Drug Delivery Systems. Int. J. Pharm. Clin. Res. 2009; 1(1): 10-14.
60. Patel AR, Patel DA, Chaudhry SV. Mucoadhesive buccal drug delivery system. Int. J. Pharm. life Sci. 2011; 2(6): 848-856.
61. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as controlled drug delivery systems. Int. J. Pharm. 2003; 255: 13-32.
62. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate systems for oral delivery to gastrointestinal tract. Adv. Drug Del. Rev. 1998; 34: 191-219.
63. Kamath KR, Park K. Mucosal adhesive preparations, In Encyclopedia of pharm. Tech. 1995; 12: 132-162.
64. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Rao YR, Polymers for mucoadhesive drug delivery system: A current status. Drug Dev. Ind. Pharm. 2008; 34:1246–1266.
65. Lehr CM, Poelma FGJ, Junginger HE, Tukker JJ. An estimate of turnover time of intestinal mucus gel layer in the rat in situ loop. Int. J Pharm. 1991; 70: 235-240.
66. Lehr CM. From sticky stuff to sweet receptors-achievements, limits and novel approaches to bioadhesion. Eur. J. Drug Meta. Pharm. 1996; 21: 139-148.
67. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int. J. Pharm. 1992; 78: 43-48.
68. Devarajan PV, Adani MH. Oral Transmucosal Drug delivery in Controlled and Novel Drug Delivery by Jain NK. 1st ed. New Delhi: CBS publishers.
69. Chien YW. Mucosal Drug Delivery: Potential Routes for Noninvasive Systemic Administration. Novel Drug Delivery Systems. 2nd ed. Marcel Dekker; 1999; 50:197-228.
70. Khar K, Ahuja A, Javed A: Mucoadhesive Drug Delivery, Controlled and Novel Drug Delivery by Jain NK. 1st ed. New Delhi: CBS publishers; 1997.
71. Patil SB, Murthy RSR, Mahajan HS, Wagh RD, Gattani SG. Mucoadhesive polymers: Means of improving drug delivery. Pharma Times. 2006; 38(4): 25-28.
72. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharm. Biopharm. 2009; 71: 505–518.
73. Sakkinen M, Marvola J, Kanerva H, Lindevall K, Ahonen A, Marvola M. Are chitosan formulations mucoadhesive in the human small intestine? An evaluation based on gamma scintigraphy. Int. J. Pharm. 307, 2006, 285–291.
74. Lehr CM. Bouwstra JA., Kok W, De Boer AG., Tukker JJ., Verboet JC., Breimer DD., Junginger HE. J. Pharm. Pharmacol. 1992; 44: 402.
75. Matharu RS, Sanghavi NM. Novel drug delivery system for captopril. Drug Dev. Ind. Pharm. 1992; 18:1567-74.
76. Krauland A, Guggi D, Bernkop SA. Oral insulin delivery: the potential of thiolated chitosan–insulin tablets on non-diabetic rats. J. Control Rel. 2004; 95: 547–555.
77. Patel VM, Prajapati BG, Patel MM. Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. AAPS Pharm. Sci. Tech. 2007; 8 (1): 147-154.
78. Hoogstraate JJ, Wertz P, Wertz P. Drug delivery via the buccal mucosa. Pharm. Sci. Tech. 1998; 1: 309–316.
79. Saettone M, Salminen L. Ocular inserts for topical delivery. Adv. Drug Deliv. Rev. 1995; 95: 95–106.
80. Nakamura K, Maitani Y, Lowman A, Takayama K, Peppas N, Nagai T. Uptake and release of budesonide from mucoadhesive, pH-sensitive copolymers and their application to nasal delivery. J. Control Rel. 1999; 61: 329–335.
81. Soane RJ, Frier M, Perkins AC, Jones NS, Davis SS , Illum L. Evaluation of the clearance characteristics of bioadhesive systems in humans. Int. J. Pharm. 1999; 178: 55–65.
82. Krauland A, Guggi D, Bernkop SA. Thiolated chitosan microparticles: A vehicle for nasal peptide drug delivery. Int. J. Pharm. 2006; 307: 270–277.
83. Alpar HO, Somavarapu S, Atuah KN, Bramwell VW. Biodegradable mucoadhesive particulates for nasal and pulmonary antigen and DNA delivery. Adv. Drug Deliv. Rev. 2005; 57: 411–430.
84. Carlfors J, Edsman K, Petersson R, Jornving K. Rheological evaluation of Gelrite in situ gels for ophthalmic use. Eur. J. Pharm. Sci. 1998; 6: 113–119.
85. Wei G, Xu H, Ding P, Li S, Zheng J. Thermosetting gels with modulated gelation temperature for ophthalmic use: the rheological and gamma scintigraphic studies. J. Control Rel. 2002; 83: 65–74.
86. Valenta C, Kast C, Harich I, Bernkop-Schnürch A. Development and in vitro evaluation of a mucoadhesive vaginal delivery system for progesterone. J. Control Rel. 2001; 77: 323–332.
87. Robinson J, Mlynek G. Bioadhesive and phase-change polymers for ocular drug delivery. Adv. Drug Deliv. Rev. 1995; 16: 45–50.
88. Leede LGJ, Boer AG, Portzgen E, Feijen J, Bremier DD. J. Control. Rel. 1986; 4: 17
89. Alexander A, Ajazuddin, Giri T, Swarna, Shukla P. Various evaluation parameters used for the evaluation of different mucoadhesive dosage forms: A Review. Int. J. Drug Form. Res. 2011; 2(2): 1-26.
90. Trivedi UM, Patel VM, Mahajan A, Mitesh P. A review on mucoadhesion, mucoadhesive polymer and mucoadhesive site. Int. J. Institutional Pharm. Life Sci. 2011; 1(2): 1-18.
91. Khairnar GA, Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymers. Int. J. Pharm. Tech. Res. 2010; 2(1): 719-735.

How to cite this article:
Sharma D, Singh M, Kumar D and Singh G. Novel Paradigms in Mucoadhesive Drug Delivery System. *Int J Pharm Sci Res* 2012; Vol. 3(7): 2455-2471.