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A REVIEW ON MUCOADHESION , MUCOADHESIVE POLYMER AND MUCOADHESIVE SITE

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ABSTRACT

Keywords:

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route

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The current article focuses on the principles of mucoadhesive drug delivery systems based on adhesion to biological surfaces that are covered by mucus. Bioadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then the phenomena is known as mucoadhesion. Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effect. Mucoadhesion is defined as the ability of material adheres to biological tissue for an extended period of time. Mucoadhesive dosage forms extend from the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery systems. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties. Evaluation of such mucoadhesive formulations has transgressed from first-generation charged hydrophilic polymer net-works to more specific second-generation systems based on lectin, Thiol and various other adhesive functional groups. Various theories are consider like Electronic theory, Wetting theory, Absorption theory, Fracture theory in mucoadhesion. Various In vitro and in vivo test carried out for determination of mucoadhesion. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc .

1. Introduction:

Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces.¹

It consists of the incorporation of adhesive molecules into some kind of pharmaceutical formulation intended to stay in close contact with the absorption tissue, releasing the drug near to the action site, thereby increasing its bioavailability and promoting local or systemic effects^{2,3}.

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface.⁴

In biological systems, four types of bioadhesion could be distinguished^{5,6}

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.

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. Bioadhesion can be modeled after a bacterial attachment to tissue surfaces, and mucoadhesion can be modeled after the adherence of mucus on epithelial tissue⁷.

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). In general, the delivery of a drug requires some type of dosage form, present in the oral cavity, to release a drug, which then diffuses through the mucosa into the local blood circulation and is then taken further to the systemic blood circulation. Buccal drug delivery has several advantages over peroral delivery. Administration of compounds via the mucosa of the oral cavity avoids pre-systemic metabolism in the gastrointestinal (GI) tract and hepatic firstpass elimination. In addition, the buccal mucosa is a well-vascularized tissue and is easily accessible for both application and removal of a delivery device. It's having facility to include permeation enhancer/enzyme inhibitor or pH-modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.⁸

Adhesion as a process, simply defined as the “fixing” of two surfaces to one another.⁹

Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers within pharmaceutical formulations along with the active pharmaceutical ingredient (API). The rationale being that the formulation will be ‘held’ on a biological surface for localised drug delivery. The API will be re-leased close to the site of action with a consequent enhancement of bioavailability.³

2. Theories of Mucoadhesion:

Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism.¹⁰

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon)^{11,12}
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration)^{11,12}

2.1. Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.¹³

2.2. 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 (Figure 1). 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 substrate¹⁰

Therefore the contact angle(θ), which may be easily determined experimentally, is related to interfacial tension (γ), of both components using

$$\gamma_{SG} = \gamma_{SL} + \gamma_{LG} \cos \theta \quad \text{eq.(1)}$$

$$S = \gamma_{SG} - (\gamma_{SL} - \gamma_{LG}), \quad \text{eq. (2)}$$

Where γ_{LG} is liquid–gas surface tension, γ_{SL} is solid–liquid surface tension and γ_{SG} is solid–gas surface tension.

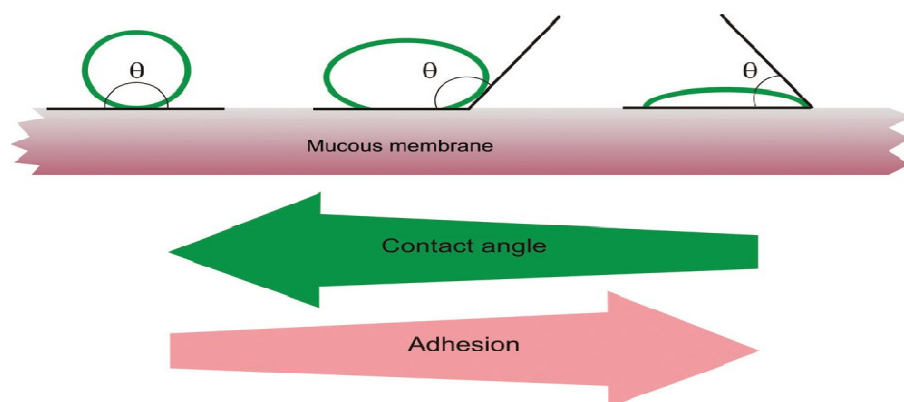


Figure 1– Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion

2.3. Diffusion Theory

This theory 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 (Figure 2). Although there are many factors involved in such processes, the fundamental properties that significantly influence this intermovement are molecular weight, cross-linking density, chain mobility/flexibility and expansion capacity of both networks.¹⁴

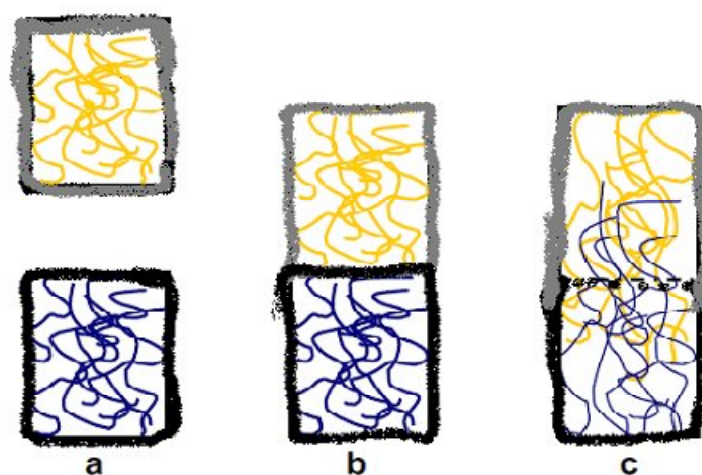


Figure 2: The diffusion theory of adhesion. (a) Top (polymer) layer and bottom (mucus) layer before contact; (b) top layer and bottom layer immediately after contact; (c) top layer and bottom layer after contact for a period of time

2.4. Adsorption Theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak vander waals forces and hydrogen bond formation. It is one of the most widely accepted theories of bioadhesion.^{15, 16}

In this instance, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate.

Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic Bonding, which is generally undesirable due to their permanency⁹. Secondary bonds arise mainly due to vander Waals forces, hydrophobic interactions and hydrogen bonding. Whilst 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 semipermanent bonds¹⁷.

2.5. Fracture Theory

This is by far the most accepted theory on bioadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum Tensile stress(S_m) produced during detachment as follows¹³.

$$S_m = F_m / A_o \quad \text{eq.(3)}$$

Where F_m and A_o represent the maximum force of detachment and the total surface area respectively. In a uniform single-component system, fracture strength (S_f), which is equal to the maximum stress of detachment (S_m), is proportional to the fracture energy (g_c), Youngs modulus of elasticity (E) and the critical crack length (c) of the fracture site as follows¹⁸

$$S_f = (g_c E / c)^{1/2} \quad \text{eq.(4)}$$

fracture energy can be obtained by the sum of the reversible work of adhesion, W_r (work done to produce new fracture surfaces) and the irreversible work of adhesion, W_i (work of plastic deformation),

$$g_c = W_r + W_i \quad \text{eq.(5)}$$

3. Mechanism of Mucoadhesion:

The mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Figure 3). 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 layer²

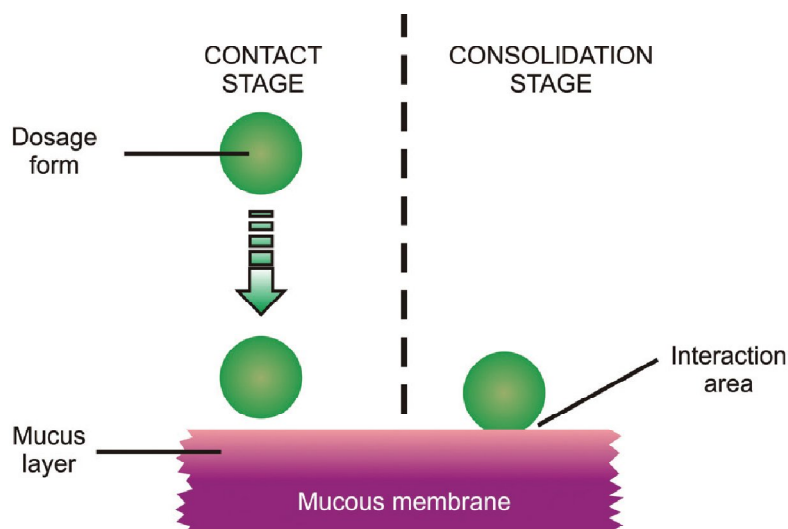


Figure 3 : Mechanism of mucoadhesion

In the consolidation step (Figure 3), 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 bonds¹. 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 bonds¹. For this to take place the mucoadhesive device has features favoring both chemical and mechanical interactions.

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 formulation or highly hydrated form.

4. Mucoadhesive Polymer

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: Polys meaning many, and meros meaning parts. Many Studies showed that addition of various polymers to Drug Delivery System, such as gums, increased the duration of attachment of the Medicinal Formulations to the mucous surface and increased the efficacy of antibiotic treatment .¹⁹

4.1 Ideal Characteristics of a Mucoadhesive Polymer

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- It Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- It Should adhere quickly to mucosa and should possess sufficient mechanical strength.
- It Should possess peel, tensile and shear strengths at the bioadhesive range
- Polymer must be easily available and its cost should not be high.
- It Should show bioadhesive properties in both dry and liquid state.
- It Should demonstrate local enzyme inhibition and penetration enhancement properties.
- It Should demonstrate acceptable shelf life.
- It Should have optimum molecular weight.
- It Should possess adhesively active groups.
- It Should have required spatial conformation.
- It Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- It Should not aid in development of secondary infections such as dental caries.

4.2 Classification of Mucoadhesive Polymer^{10, 11,12,20,21}

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 categorise 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

Hydrophilic polymers

Hydrogels

Hydrophilic polymers Contains carboxylic group and possess excellent mucoadhesive properties.

These are PVP(poly vinyl pyrrolidone)

Mc(methyl cellulose)

Scmc(sodium carboxy 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^{22- 25}

They can also be classified as,²⁶

Synthetic polymers

Natural polymers

Synthetic polymers - Cellulose derivatives, Carbopols, etc.

Natural polymers- Tragacanth, Pectin, Gelatin, Sodium alginate, Acacia

4.3 Newer second generation polymers¹⁰

They have the following advantages:

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

Lectins²⁷

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

Thiolated polymers²⁸

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 cysteine 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.

For example:

- ✓ chitosan iminothiolane
- ✓ Alginate cysteine

5. Factors Affecting Mucoadhesion :

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.²⁹

1. Polymer based factors

- ✓ Molecular weight of the polymer
- ✓ Concentration of polymer used
- ✓ Flexibility of polymer chains
- ✓ Swelling factor
- ✓ Stereochemistry of polymer

2. Physical factors

- ✓ pH at polymer substrate interface
- ✓ Applied strength
- ✓ Contact time

3. Physiological factors

- ✓ Mucin turnover rate
- ✓ Diseased state

6. Possible Mucoadhesive Site for 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. Due to mucoadhesion certain water-soluble polymers become adhesive on hydration³⁰ and hence can be used for targeting a drug to a particular region of the body for extended periods of time.³¹ The mucosa lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose, and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may include the following:³²

1. Gastrointestinal delivery system.
2. Nasal delivery system.
3. Ocular delivery system.
4. Buccal delivery system.
5. Vaginal delivery System.
6. Rectal delivery system.

6.1. Gastrointestinal drug delivery system:

The idea of mucoadhesive began with the clear need to localize a drug at certain sites in the GI tract. 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.

Decrosta et al.³³ also used carbopol 934P as mucoadhesive substance to prepare captopril sustained-release tablets. Captopril mixed with carbopol 934P and stearic acid (as lubricant), tableted, could sustain the release of the drug for up to 16 hours or more.

6.2. Nasal drug delivery system:

Histologically the nasal mucosa provides a potentially good route for systemic drug delivery. With a surface area of 150 cm², a highly dense vascular network, and a relatively permeable membrane structure, the nasal route has good absorption potential. One of the most important features of the nasal route is that it avoids first-pass hepatic metabolism, thereby reducing metabolism.

The use of dry powder formulations containing mucoadhesive polymers for nasal administration of peptides and proteins was first investigated by Nagai et al.³⁴

6.3. Ocular drug delivery system:

Mucin is secreted by conjunctival goblet cells, but there are no goblet cells on the cornea. On this basis, a mucoadhesive polymer will firmly attach to conjunctival mucus but only loosely, if at all, to corneal mucus.^{35, 36} Ophthalmic dosage forms can be improved by increasing the time the active ingredients remain in contact with eye tissues. There are several mucoadhesive dosage forms that have been developed to this end: liquid systems, in situ gelling systems, dispersed, systems and solid systems.^{37 - 43}

6.4. Buccal drug delivery system:

Because of the presence of a smooth and relatively immobile surface for placement of a mucoadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using mucoadhesive systems. The buccal and sublingual routes avoid first-pass metabolism. These regions consist of a non keratinized epithelium, resulting in a somewhat more permeable tissue than the skin. Therefore, drugs with a short biological half life requiring a sustained release effect and exhibiting poor permeability, sensitivity to enzymatic degradation, or poor solubility may be good candidates to be delivered via the oral cavity. Relevant mucoadhesive dosage forms for the oral cavity include gels, patches, tablets, and ointments,⁴⁴⁻⁴⁸.

Nagai et al⁴⁹ Formulated a highly viscous gel containing carbopol and hydroxypropyl cellulose for ointment dosage forms that were maintained on the tissue for up to 8 hours.

7. Evaluation of Mucoadhesive Dosage forms:

7.1 In vitro tests / Ex vivo⁵⁰

- ✓ Methods determining tensile strength
- ✓ Methods determining shear stress
- ✓ Adhesion weight method
- ✓ Fluorescent probe method
- ✓ Flow channel method
- ✓ Mechanical spectroscopic method
- ✓ Falling liquid film method
- ✓ Colloidal gold staining method

- ✓ Viscometer method
- ✓ Thumb method
- ✓ Adhesion number
- ✓ Electrical conductance
- ✓ Swelling properties
- ✓ In vitro drug release studies
- ✓ Muco-retentability studies

7.2 In vivo methods⁵¹

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

7.1 In vitro method:

7.1.1. Falling Liquid Film method:

Nielsen, Schubert and Hansen (1998) used a method proposed by Rango Rao and Buri (1989) in which the chosen mucous membrane is placed in a stainless steel cylindrical tube, which has been longitudinally cut. This support is placed inclined in a cylindrical cell with a temperature controlled at 37 °C. An isotonic solution is pumped through the mucous membrane and collected in a beaker. Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter. For semi-solid systems, the non adhered mucoadhesive can be quantified by high performance liquid chromatography. This methodology allows the visualization of formation of liquid-crystalline mesophase on the mucous membrane after the flowing of the fluids and through analysis by means of polarized light microscopy.^{52,53,54}

7.1.2 Swelling index⁵⁵⁻⁵⁸

Swelling of formulation excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting

in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the dosage form.

Method:

For each formulation batch, one formulation was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the dosage form was removed from beaker and weighed again up to 8 hours. The swelling index was calculated using following formula.

$$\text{Swelling Index (S.I.)} = (W_t - W_o) / W_o \quad \text{eq.(6)}$$

Where, S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before placing in the beaker

7.1.3. Mucoadhesive Strength⁵⁹

Mucoadhesive strength of the dosage form was measured on the modified physical balance. The design used for measuring the mucoadhesive strength was shown in Figure 4. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCl pH 1.2, which was then placed below right side of the balance. Goat or rat stomach mucosa was used as a model membrane and buffer media 0.1N HCl pH 1.2 was used as moistening fluid.

The one side of the dosage form was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive dosage form was established. A preload of 10 mg was placed on the slide for 5 min (preload time) to established adhesion bonding between mucoadesive dosage form and goat or rat stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive dosage form was detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} \times 9.81 \quad \text{eq. (7)}$$

1000

$$\text{Bond strength (N/m}^2\text{)} = \text{Force of adhesion (N)} / \text{Surface area of tablet (m}^2\text{)} \quad \text{eq. (8)}$$

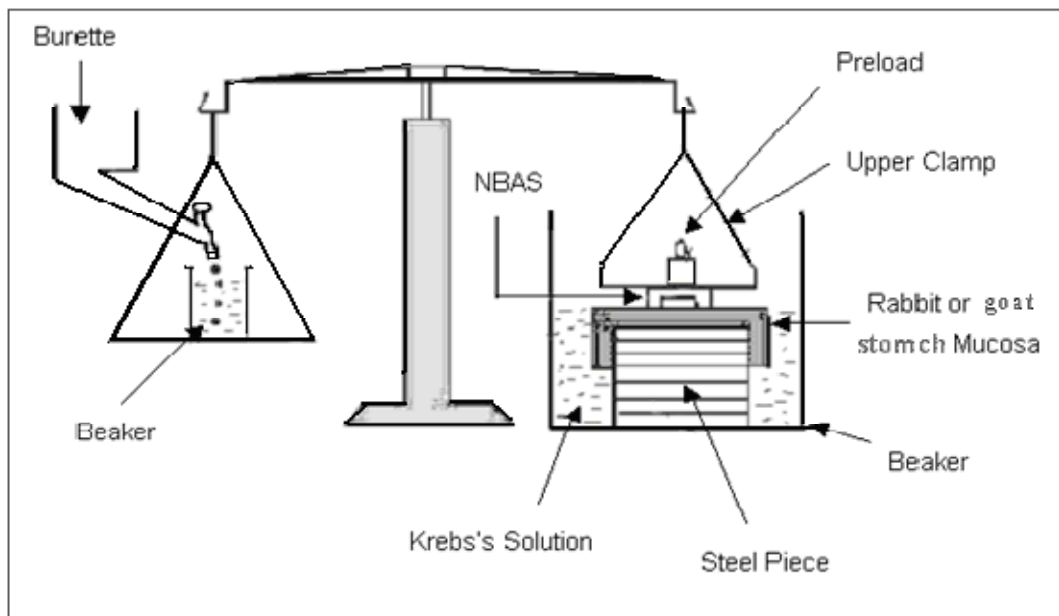


Figure : 4 : Mucoadhesion Test Assembly

8. Conclusion:

Mucoadhesive dosage forms 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. The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. The factors which are determinant in the overall success of the mucoadhesive drug delivery are the polymer physicochemical properties and the in-vivo factors such as the mucin turn over rate, mucin flow. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa.

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