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A REVIEW ARTICLE ON MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT: As an alternative to injection pharmaceutical researcher and scientist are trying to explore transdermal and transmucosal route over the last few years. To overcome the deficiency associated with the other route of administration buccal region of oral cavity is an alternative target for the administration of choice of drug. The disadvantages relative with the oral drug delivery is the extensive presystemic metabolism, instability in acidic medium as a result inadequate absorption of the drugs. However parental route may overcome the drawback related with the oral route but these formulations have high cost, supervision is required and least patient compliance. By the buccal route the drug are directly pass through into systemic circulation, less hepatic metabolism and high bioavailability. The aim of the review article is an overview of buccal drug delivery, anatomy of oral mucosa, mechanism of drug penetration and their *in-vitro* and *in-vivo* mucoadhesion testing method.

INTRODUCTION: Amongst the various routes of drug delivery, oral route is mostly preferred by the patient. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism many drugs, cannot be delivered effectively through the conventional oral route, because after administration are subjected to pre-systemic clearance extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability [1, 2, 3].

The oral route of drug administration is divided into several types. But this route also have some disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins, and buccal drug delivery is one of the a good alternative amongst the various routes of drug delivery. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery.

Buccal routes of drug delivery offer a large number of advantages over the other route of drug administration for systemic drug delivery such as bypass of first pass effect and drug directly delivered to systemic circulation, avoidance of pre-systemic elimination within the GI tract. These factors make the buccal drug delivery a very attractive and feasible site for systemic drug delivery.

Considering the other routes of drug delivery which has low patient compliance such as rectal, vaginal, sublingual and nasal drug delivery for controlled release, the buccal mucosa has rich blood supply and it is relatively permeable [4]. The researcher group has been investigated that nasal cavity as a site for systemic drug delivery but the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage form put this route in the second line of drug delivery. Even though the rectal, vaginal, and ocular mucosae all offer certain advantages, but the poor patient acceptability associated with these sites renders them

reserved for local applications rather than systemic drug administration [1, 2, 5]. The buccal have ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. The buccal mucosa are rich in blood supply and absorption occur at this place is efficient, and additionally the route also providing rapid drug transport to the systemic circulation and avoiding degradation by gastro-intestinal enzymes and first pass hepatic metabolism [4].

Moreover, the oral cavity is easily accessible for self medication and the administration drug is to be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. Buccal mucosa is less permeable than the sublingual site which makes it more appropriate choice of site if prolonged drug delivery [6].

Mucoadhesive Drug Delivery System in Oral Cavity [4, 7]: Drug delivery via the membranes of the oral cavity can be subdivided as follows:

1) **Sublingual Delivery:** drugs are delivered through mucosal membrane lining the floor of mouth into systemic circulation.

2) **Buccal Delivery:** drugs are delivered through mucosal membrane into systemic circulation by placing drug in between cheeks and gums.

3) **Local Delivery:** drugs are delivered into the oral cavity.

Classification of Buccal Bioadhesive Dosage Forms: [5, 8]

1. Buccal Bioadhesive Tablets.
2. Buccal Bioadhesive semisolids.
3. Buccal Bioadhesive patch and films.
4. Buccal Bioadhesive Powders.

1. **Buccal Bioadhesive Tablets:** Buccal bioadhesive tablets are dry dosage forms that are to be moistened after placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. These tablets are solid dosage forms that ate prepared by the direct compression of powder and can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form. They can deliver drug multi-directionally into the oral cavity or to the mucosal surface.

2. **Buccal Bioadhesivc Semisolid Dosage Forms:** Buccal bioadhesive semisolid dosage forms consist of finally powdered natural or synthetic polymers dispersed in a polyethylene or in aqueous solution example: Arabase.

3. **Buccal Bioadhesive Patches and Films:** Buccal bioadhesive patches consists of two ply laminates or multilayered thin film that are round or oval in shape, consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films arc formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

4. **Buccal Bioadhesive Powder Dosage Forms:** Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa the reduction in diastolic B.P after the administration of buccal tablet and buccal film of Nifedipine.

Advantages of Buccal Drug Delivery System [7, 9, 10, 11, 12, 13, 14]

1. The residence time of dosage form at the site of absorption is prolong, hence increases the bioavailability.
2. Rapid onset of action.
3. High blood supply and good blood flow rate cause rapid absorption.
4. In the acidic medium of git drug is protected from degradation.
5. Improved patient compliance.
6. Nor painful neither irritations.

Disadvantages of Buccal Drug Delivery System:

1. Prolonged contact of the drug possessing ulcerogenic property.

2. For the *in vitro* screening of drugs the oral mucosal delivery is lack of good model. This is the major drawback of this drug delivery.

3. Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.

4. As compared to the sublingual membrane the buccal membrane is low permeability.

5. Also has smaller surface area.

6. The dissolution of drug due to continuous secretion of saliva (0.5-2 l/day).

The basic components of buccal bioadhesive drug delivery system are [4, 15]:

1. Drug substance
2. Bioadhesive polymers
3. Backing membrane
4. Penetration enhancers

1. **Drug substance:** The drug substances are decided on the basis of, does drug used for rapid release/prolonged release and for local/systemic effect? Before formulating buccoadhcsive drug delivery systems, one has to decide whether the intended. The drug should have following characteristics;

   1. The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
   2. The conventional single dose of the drug should be small.
   3. The drug absorption should be passive when given orally.
   4. Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
   5. Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

2. **Bioadhesive polymers:** The second step in the development of buccoadhcsive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation." Bioadhesive polymers play a major role in buccoadhcsive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs an ideal polymer for buccoadhcsive drug delivery systems should have following Characteristics.

   1. It should be inert and compatible with the environment
   2. The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
   3. It should adhere quickly to moist tissue surface and should possess some site specificity.
   4. The polymer must not decompose on storage or during the shelf life of the dosage form.
   5. The polymer should be easily available in the market and economical.

3. **Backing membrane:** Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. The commonly used materials in backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc. The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers.

4. **Penetration enhancers** [4, 16, 17, 18, 19, 20, 21]: To increases the permeation rate of the membrane of co-administrated drug they are added in the pharmaceutical formulation. Without causing toxicity and damaging the membrane they improve the bioavailability of drugs that have poor membrane penetration. The capability to enhance the penetration is depend upon they are used in combination or alone, nature of vehicle,

physiochemical propertied of drug and site of administration (**Table 1**).

TABLE 1: MUCOSAL PENETRATION ENHANCERS AND MECHANISMS OF ACTION [4, 16, 17, 18, 19, 20, 21]

Sr. No	Classification	Examples	Mechanism
a.	**Surfactants**	**Anionic:** Sodium lauryl, sodium lauryl **Cationic:** cetylpyridinium chloride **Nonionic:** poloxamer, brij, span, myrj, tween **Bile salts:** sodium gylcodeoxycholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate azone.	Perturbation of intercellular lipid, protein domain integrity
b.	**Fatty acid**	Oleic acid, ceprylic acid.	Increase fluidity of phospholipid domains
c.	**Cyclodextrains**	α, β, γ, cyclodextrin, methylated β –cyclodextrins.	Inclusion of membrane Compounds
d.	**Chelators**	EDTA,sodium citrate.	Interfere with Ca Polyacrylates
e.	**Positively charged polymers**	Chitosan, trimethyl chitosan.	Ionic interaction with negative charge on the mucosal surface
f.	**Cationic compound**	Poly-L-arginine, L-lysine.	Ionic interaction with negative charge on the mucosal surface

Anatomy of the Oral Cavity [4, 7, 8, 10, 22, 23]:

The Oral Cavity: The oral cavity is divided into two regions the lips and cheeks bound the outer oral vestibule and oral cavity formed by hard and soft palates, the floor or mouth and tonsils. The oral cavity is lined by a multilayered mucous membrane of a highly-vascularized nature relatively thick and dense. Under the mucous membrane there are net of capillaries and arties from which drug is penetrating into the systemic circulation. Inside the cheeks there is a lining of membrane that is buccal mucosa, and term "buccal drug delivery" refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingival.

Overview of Buccal Mucosa: Oral mucosa is dividing into two part epithelium and basement membrane and connective tissue.

A) **Epithelium:** The epithelium serves as a protecting covering for the tissue and a barrier to the entry of foreign particle. It has thickness 500-800µm and consists of 40-50 layers of stratified sqamous epithelial cell.

B) **Basement membrane and connective tissue:** Basement membrane is a boundary between the basal layer of epithelium and connective tissue. It consists of extracellular materials. The organisation which determines the mechanical stability, resistance to deformation, extendibility of tissue is made up of bulk of connective tissue.

The Mucus Layer: To the mucosal epithelial surface a translucent and viscid secretion which is a thin, continuous gel blanket are adherent called as mucus. In the human the mean thickness of this layer varies from about 50 to 450µm. The goblet cells lining the epithelia or by special exocrine glands that secreted mucus. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathphysiological state. However, it has the following general composition

1. Water - 95%
2. Glycoprotein's and Lipids - 0.5 to 5%
3. Mineral salts - 0.5 to 1%
4. Free Proteins - 0.5 to 1%

Functions of mucus layer: Act as a protective, barrier, adhesion and lubrication.

Physiological factors affecting buccal bioavailability

1. **Inherent permeability of the Epithelium:** The epithelium is a specialized barrier function and highly specialized for absorption functions and the epithelium play a key role of permeability in between the skin epithelium. The sublingual mucosa is more permeable than the buccal mucosa in the oral cavity.
2. **Thickness of Epithelium:** The thickness of buccal mucosa is near about 500-800µm. And this thickness is varies at different sites of oral cavity.

3. **Blood supply:** The drugs moieties are absorbed in the systemic circulation due to presence of lymphatic network in the lamina propria and rich in blood supply. The blood flow in the buccal mucosa is 2.4ml min^{-1}cm.

4. **Metabolic activity:** Avoidance of first pass metabolism of drug at liver and gut wall because the drug are directly delivered to the blood. For the drugs that are enzymatically labile such as proteins and peptide are delivered by this route.

5. **Saliva and mucus:** The salivary gland secret daily saliva 0.5-2L that constantly wash the oral mucosa. The increases in the bioavailability due to presence of lot of saliva in the sublingual area which enhance the dissolution rate of the drugs.

6. **Ability to retain delivery system:** The buccal mucosa is used for the retentive drug delivey system because it is smooth and relatively immobile.

7. **Transport routes and mechanisms:** There are two routes via which drug permeate across the epithelia barrier is:

   - The paracellular route: between adjacent epithelial cells.
   - The transcellular route: the drug transfer by the mechanism such as passive diffusion, carrier mediated transport and via endocytic process, across the epithelial cells.

Mechanism of Mucosal Adhesion [21, 23, 24, 25]: Several theories purposed the mechanism of mucoadhesion by the interaction of polymer and mucus. The mechanism of mucoadhesion is divided into two steps, first is contact step and second is consolidation step. In the first step the mucus layer come in contact with mucoadhesive and mucous membrane and the formulation swell and spread over mucus membrane. In the second consolidation step the moisture activates the mucoadhesive material, this plasticizes the system, this allow to mucoadhesive molecules to break free and link up by weak Vander walls and hydrogen bonds. The diffusion and dehydration theory explain the consolidation step.

The diffusion theory is the mutually interacting of mucoadhesive molecules and glycoprotein of mucus and building of secondary bonds by interpenetration of their chains (**Fig. 1**).

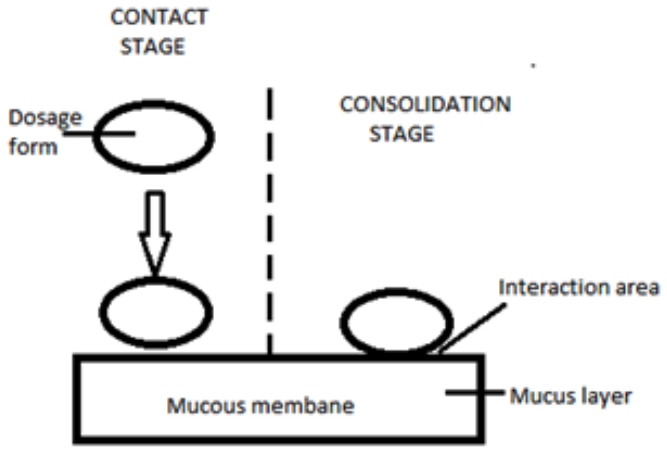


FIG. 1: TWO STEP OF MUCOADHESION PROCESS

According to the dehydration theory the material get gelify when it come in contact with the mucus in the aqueous environment. The drawing of water into the formulation due to concentration gradient until the osmotic balance is reached. This process increases the contact time of mucous membrane with the mixture of formulation and mucus. So it is not the interpenetration of macromolecules chains, it is the water motion that lead to the consolidation of the adhesive bond. The dehydration theory is not applicable for highly hydrated forms or solid formulations (**Fig. 2**).

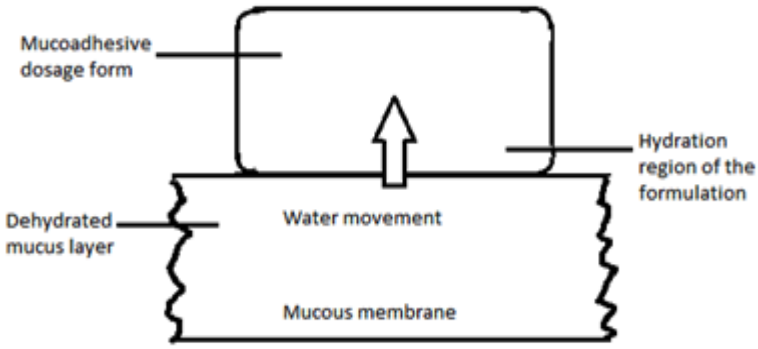


FIG. 2: DEHYDRATION THEORY OF MUCOADHESION

Theories of Mucoadhesion [21, 23, 25]:

1. **Electronic Theory:** This theory is based on the opposing electrical charge of mucoadhesive and biological material. The transfer of electron takes place when both the material comes in contact and building of double electronic layer at the

surface. And the mucoadhesive strength is determined by the attractive forces within the electronic double layer.

2. **Adsorption Theory:** According to this theory, by the secondary chemical interaction such as vander Walls and hydrogen bond, electrostatic attraction or hydrophobic interactions the mucoadhesive material adheres to the mucus. For example the polymer contain carboxyl group the hydrogen forces are the prevalent interfacial forces.

3. **Wetting Theory:** This theory applies to those liquid systems which present affinity to the surface in order to spread over it. The contact angle is a measuring technique used to find the affinity. It is a general rule that greater be the affinity lower the contact angle. For the adequate speadability the contact angle must be equal or close to zero. By taking difference between surface energy γ_B and interfacial energy γ_A the spreadability coefficient is calculated. The equation is:

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

If greater the interfacial energy in relating to the individual surface energy, greater the adhesion work W_A, i.e., greater the energy needed to separate the two phases.

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

4. **Diffusion Theory:** The essence of this theory is that to create a semi permanent adhesive bond the substrates interpenetrate one another to a sufficient depth. The diffusion co-efficient is depend on molecular weight and cross-linking density and the penetration rate depends on the diffusion coefficient of both interacting polymers. In addition the parameter to be consider are segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network.

5. **Fracture Theory:** For measurement of the mucoadhesion mechanism this is most studied theory. This theory is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon./L)\ ½.$$

Where: E- Young's modules of elasticity ε- Fracture energy L- Critical crack length when two surfaces are separated.

Bioadhesive Polymers [1, 4, 5, 14]: Mucoadhesive polymers are the important component in the development of buccal delivery systems. The first step in the development of buccoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation. Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs**.** Bioadhesive polymers have properties to get adhered to the biological membrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance. Mucoadhesive polymers used in the oral cavity were shown in **Table 2**.

Classification of mucoadhesive polymers used in oral cavity is presented in Table**:**

TABLE 2: MUCOADHESIVE POLYMERS USED IN THE ORAL CAVITY [4, 19, 26]

Criteria	Categories	Examples
Source	Seminatural/Natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Synthetic	**Cellulose derivatives** CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, Methyl hydroxyl ethyl cellulose] **Poly(acrylic acid)-based polymers** [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acidco-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate),poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG] **Others:** polyoxyethylene, PVA, PVP, thiolated Polymers

Aqueous Solubility	Water-soluble	CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate,sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive Forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic Interaction	Chitosan

Ideal characteristics of Buccal Adhesive Polymers:

1) Polymer and its degradation products should be non-toxic, non-irritant and non-absorbable in the gastrointestine tract.
2) The polymer should have good properties like wetting, swelling, solubility and biodegradability properties.
3) The polymer should show sufficient mechanical strength by adhere quickly to the buccal mucosa.
4) The polymer should show sufficient tensile and shear strengths at the bioadhesive range.
5) Polymer should not be of high cost and must be easily available.
6) The polymer must have bioadhesive properties in both dry and liquid state.
7) The polymer should have properties like penetration enhancement and local enzymatic inhibition.
8) The polymer does not decompose during the shelf-life of dosage form and during storage.
9) Should have narrow distribution and optimum molecular weight.
10) The polymer should not have degree of suppression of bond forming group but should have sufficient cross-linkage.
11) Should not produce the secondary infection in the dental caries.

Reported Buccoadhhesive Drug Delivery System (Table 3):

TABLE 3: REPORTED BUCCOADHHESIVE DRUG DELIVERY SYSTEM

Sr. No.	Category	Example	Dosage type	Polymer
a.	**NSAIDS**	Diclofenac sodium [27], Piroxicam [28] Flurbiprofen [29]	Tablet	Cashnew nut tree gum, HPMCK4M, Carbopol, Chitosan, Sodium CMC
b.	**Anti-Hypertensive**	Dilitiazam hydrochloride [30], Lisinopril [31], Metoprolol tartrate [32], Losartan potassium [33], Propranolol hydrochloride [34], Timolol maleate [35].	Tablet	Carbopol-934P, Sodium CMC, HPMCK4M, Sodium alginate, guar-gum, HEC, Xanthane gum,
c.	**Anti-emetic**	Domperidom [36], Granisetron hydrochloride [37]	Tablet	Carbopol934P, Metocel K4M, Chitoan, Sodium alginate, HPMC 50cps
d.	**Anti-diabetic**	Rapaglinide [38]	Tablet	Carbopol 934P, HPMC, Sodium CMC, HEC.
e.	**Bronchodilator**	Salbutamol sulphate [39]	Tablet	Carbopol 934P, HPMC K4M, Chitosan
f.	**Vasoconstrictor**	Sumatriptan [40]	Tablet	Chitosan, HPMC K4M, Sodium alginate.
g.	**Anti-viral**	Acyclovir [41]	Tablet	Carbopol 943P, HPMC K100M

Techniques for the evaluation of Mucoadhesive Polymer: Techniques used for the evaluation of mucoadhesive drug delivery system:

A) *In-vitro* method

1. **Tensile stress measurement:**

(a) Wilhelmy plate technique [42]: This method is used to measure the mucoadhesive strength. In this method the glass plate is dipped into the mucoadhesive polymer solution. The animal skin such as goat intestine is used to take the mucus gel and placed the container at 37ºC. On the one side the glass plate is attached with nylon thread, and on the other side the weight is raised. At specific interval water required to pull out the glass plate from the mucus represent. And the force required the force required to break the mucus-polymer contact against adhesion. Six plates are used for the test and average is calculated (**Fig. 3**).

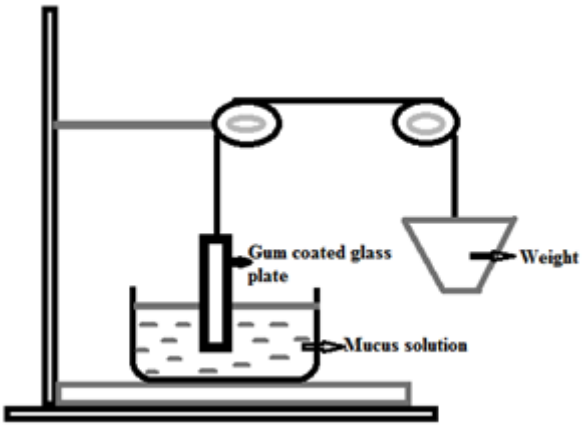


FIG. 3: WIHELMY'S METHOD

(b) Novel Electromagnetic Force Transducer (EMFT) [43]**:** From a tissue sample EMFT measure the tissue force required to detach the magnetic loaded polymer micro-carrier. The electromagnet that is mounted on microscope vertically was used to generate the magnetic force when micro-carrier was attached to the sample tissue. When tissue chamber was slowly moved down, away from the magnet trip the computer determine the position of micro-carrier. This process was continuous video until it is completly pulled free to the tissue and from this calculates the position of micro-carrier. The results are shown by plot of force vs displacement and eighter by raw data. By this technique evaluation of mucoadhesion of polymer to specific cell type can be done and also for the mucoadhesive drug delivery in tissue specific targeted.

2. **Shear Stress Measurement** [44, 45]: This method measure the force that cause a mucoadhesive to slide over the mucus layer in directional parallel to their place of contact of adhesion. The mucoadhesive test solution was prepared. Over the 3 glass plates the weighted amount of prepared solution is spread. Take another clean slide that are placed over the first plate and made to spread the polymer solution uniformly in between two glass plates by placing weight on the glass plates. Now place the glasses for some min, undisturbed then one side of glass plate was attached to a hook and the other was collected to a twin passing over a pulley and at the end of pan was attached, as shown in figure. After sometimes an increasing manner weight was placed till the plates attached with polymer got detached. At which weight it is just detached note down and the average weight was calculated as per methods official method (**Fig. 4)**.

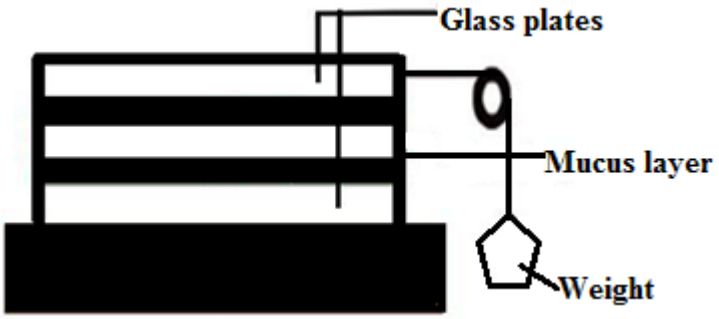


FIG. 4: SHEAR STRESS MEASUREMENT

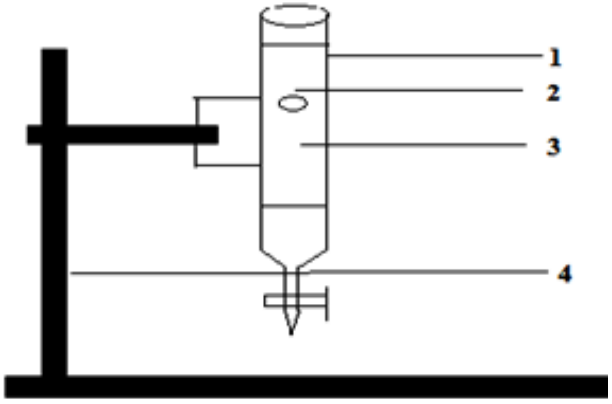
3. **Adhesion weight method** [46]: In this method the weight of adherent particle was determined by flowed a suspension of an exchange resin particles over the inner mucosal surface of a section of animal intestine (guinea pig). This method has limited value due to poor data reproducibility because rapid degradation and biological variation of the tissue. But it was possible to determine the effect of particle size and charge on the adhesion with adverted intestine after 5 minutes contact.

4. **Fluorescent Probe method** [47]: For the determination of the bioadhesive potential of large number of polymer the Fluorescent probe method is used. In the technique labelling the lipid bilayer and memberane protein with the fluorescent probes (pyrene and fluorescein isothiocynate). Addition of polymers to this substrate surface compressed the lipid bilayer or protein causing a change in fluorescence, as compared to control cells. By using this method it was possible to compare charge type, density, backbone structure and their influence on polymer adhesion.

5. **Flow Channel method** [48]: This method was developed by Mikos and Peppas. A 2% w/w aqueous solution of bovine submaxillary mucin, thermostatic at 37ºC is filled in a glass made up of thin channel. Humid air at 37ºC was passed through glass channel. The adhesion property is calculated by placing a particle of bioadhesive polymer on the mucin gel and its static and dynamic behaviour is monitored at frequent intervals using a camera.

6. **Mechanical Spectroscopic method** [49]: For the investigating the effect of pH, polymer chan length and interaction between glycoprotein gel and polyacrylic acid mechanical spectroscopy was used. Mortazavi et al., used a similar method to investigate the effect of carbopol 934 on the rheological behaviour of mucus gel. They also investigated the role of mucus glycoprotein and the effect of various factors such as polymer molecular weight and ionic concentration, and the introduction of anionic, cationic and neutral polymers on the mucoadhesive mucus interface.

7. **Falling Sphere method [50]:** The falling sphere method was used for characterize the mucoadhesive strength. In this method a clean burette was taken and filled with 10% mucus solution and fixed in a stainless steel tube. The polymer solution at various concentrations is prepared and the mustard grain which retained on sieve size # 12 were taken and dipped in this polymer solutions. After that each mustard grain slowly placed on mucus layer. Time taken by the grain to fall 50 divisions in the burette was noted and values were calculated (**Fig. 5**).



1. Glass burette (50 ml), 2. Mustard grains of uniform size, 3. Homogenized mixture of 10% mucus solution, 4. Burette stand.

FIG. 5: FALLING SPHERE METHOD

8. **Colloidal Gold Staining** [51]: In this technique, mucin gold conjugate are formed by stabilizing the red colloidal gold particle over mucin molecules, a red colour is developed on the bioadhesive hydrogel surface. By measuring the intensity of red colour on the hydrogel surface the interaction between them is easily quantified or by the measurement of the decrease in the concentration of the conjugates from the absorbance at wavelength 525nm.

9. **Viscometric method** [52]: Hassan and Gallo used simple viscometer to quantify the mucin-polymer bioadhesion bond strength. The Brookefield visometer measure the bioadhesion bond strength in the presence or absence of neutral, anionic and cationic polymers.

10. **Thumb test** [49]: Simplest test method used to quantify mucoadhesiveness. The adhesiveness is measured by the method that, the difficulty of pulling the thumb from the adhesive as a function of pressure and contact time. It is most likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesives are non-specific and not mucin specific and like mucin the skin has also many hydroxyl groups for interaction with bioadhesive systems. It provides useful information on mucoadhesive potential although the thumb test may not be conclusive,

11. **Electronic Conductance** [49]: The semisolid mucoadhesive ointments are tested by electronic conductance method. For measuring the electronic conductance we use a modified rotational viscometer. In this method the artificial membrane in the artificial saliva is used, the adhesion of orabase, carbopol, eudispert, guar gum and methylcellulose is calculated. In the presence of adhesive the conductance is comparatively low, as the adhesive was removed, the value increased to final value, which corresponds to the conductance of saliva, which indicates the absence of adhesion.

12. **Swelling index of the Natural Mucoadhesive Agent [53]:** The mucoadhesive polymer are weight and pass into #80 number sieves and placed in the petri-dish with 10ml distilled water and after every 10 mint shake it and place for 3hr at room temperature. After every 1hr the water is discarded and increased weight of mucoadhesive polymer is note down and same done for 3 hr. The mean of 3 times are calculated.

$$\text{Swelling index} = [(W_2-W_1)/W_1]$$

Were, W_1= weight of natural mucoadhesive agent before swelling W_2=weight of natural mucoadhesive agent after swelling.

13. **Detachment Force Measurement** [54]**:** This method is used to determine the mucoadhesive strength. In this method the intestine of goat is collected from slaughter house and transported to laboratory in tyrode solution (g/litter). The intestine of goat is cut from a specified area and ties it on glass slide. The one side of glass is affixed on one side floor below the modified physical balance. Mucoadhesive tablet prepared by using mucoadhesive polymer is pasted on another glass slide and it balanced in the assembled physical balance with a beaker in other side which is used to hold the water. Now the balance was calibrated.

B) *In vivo* method

1. **GI transit using Radio-Opaque Technique** [55]: In this method use of radio-opaque markers, e.g., barium sulfate, encapsulated in bioadhesive dosage to determine the effects of bioadhesive polymers on GI transit time. Faeces are collected (using an automated faeces collection machine) and x-ray inspection to monitoring total GI residence time without affecting normal GI motility. Mucoadhesive labelled with Cr-^{51}, Tc-^{99m}, In-^{113m}, or I-^{123} is used to study the transit the GI tract.

2. **Gamma Scintigraphy Technique:** It is a valuable tool used in the development of pharmaceutical dosage forms. By using this method, it is possible to obtain information non-invasively. This technique is very useful in oral dosage form and provides information across the different regions of GI tract, the time and site of disintegration of dosage forms, the site of drug absorption, and also the effect of food, disease, and size of the dosage form on the *in-vivo* performance of the dosage forms.

CONCLUSION: The buccal drug delivery provides a several advantages for the delivery of drug. The buccal mucosa is rich in both vascular and lymphatic system through which drugs are directly drainage in systemic circulation and first-pass metabolism in liver and pre-systemic elimination in gastrointestinal tract are avoided. Additionally buccal drug can be terminated in case of toxicity thereby provide a safe and easy method for administration of drugs. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery and attractive alternative for delivery of potent peptide and protein drug molecules. For the evaluation of the buccal drugs both techniques of *in-vitro* or *in-vivo* are developed. Mucoadhesive dosage forms are the extended forms of the simple oral drug delivery system with large number of advantages over it. However with the recent developments of new formulation types such as mucoadhesive preparations and the use of peptides as drugs this number may increase in the future.

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