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A REVIEW ON THE BUCCAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH OF DRUG DELIVERY

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Abstract:

Oral drug delivery is the most preferable route of drug administration due to ease of administration, Patient compliance, Flexibility in formulation etc. However, In case of the oral route there are several challenges such as First pass metabolism and drug degradation in GI environment and poor pharmacological response. Buccal route is the easy and cheap methodto prepare for oral delivery of drug. The buccal mucosa is one of the administration site that might provide an alternative for per oral administration. This route provides the direct accessesto the systemic circulation through the jugular vein bypass the first pass metabolism which leads high bioavailability. The drug having low bioavailability, shorter half life and those who undergoes extensive first pass metabolism are good candidate for this route. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. In this article various things are discussed about the buccal route of the drug delivery like about the various formulations of buccal route are Films, Tablets, Patches, Powders, Ointments & Gels and also discussed about the factors related to these formulation. In this article we also discussed about the theory of the mucoadhesion like Wetting theory, Absorption theory, Electronic theory & Fracture theory of the mucoadhesion.

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INTRODUCTION:

Buccal drug delivery system is those in which drug is deliver via mouth. In this delivery system the formulation is kept between gums and chicks and after this the drug is released from the formulation and absorb via mucosal lining of the chicks. In 1947 the first buccal drug delivery formulation was prepared. In this formulation the penicillin is absorb via mucosal lining of the chicks in which there is a mixture of gum tragacanth and dental adhesive powder. The BDDS is useful to transfer the drug into systemic circulation who have high first pass metabolism or those drugs which are degraded in the GI track. This delivery system avoids theformulation to go through the GI track. This delivery system provide rapid on set of action and formulation is removed from the mouth when it is required or when it is inconvenient to the patient.

Muco-adhesion is a situation in which two components, one of which is biological in origin,are held together by interfacial forces for lengthy periods of time.

The following are examples of mucoadhesive drug delivery systems:[1]

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system.
- Nasal delivery system
- Ocular delivery system

ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM [2]

- The buccal patches enhance the bioavailability of the drug by inhibiting hepatic firstpass metabolism.
- GI enzymes and the acidic environment helps to protect the drug from deterioration.
- Muco adhesion increases the residence time of the drug which results in bio availability enhancement.
- Self-administration is possible.
- Taste masking is possible.
- The surface area of patch is large due to this fast disintegration and dissolution of drugand it enhance the absorption of API.
- Easy to remove when it is no required.

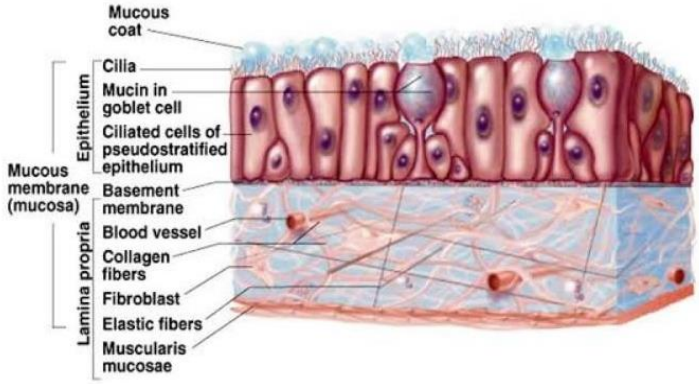
DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM [2]

- In comparison to the sublingual membrane, the buccal membrane has a modest permeability.
- Local ulcerous impact as a result of prolonged medication interaction.
- The number of drugs that can be given this way is limited due to poor skin permeability.
- Rapid medication clearance occurs as a result of salivary flushing or food ingestion.
- Acceptability by patients in terms of flavour, irritancy, and mouth feel is a problem.

Anatomy of oral mucosa [15]:

Mucus membranes (mucosa) are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestines and bronchi) or multilayered/stratified (e.g. in the esophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain,or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus can be found in two forms: a gel layer adhering to the mucosal surface and a luminal soluble or suspended form. Mucin glycoproteins, lipids, inorganic salts, and water are the primary components of all mucus gels, with the latter accounting for more than 95 percent of their weight, making them a highly hydrated system. Mucus has two main functions: protection and lubrication.

The mechanism of muco adhesion is as follows:

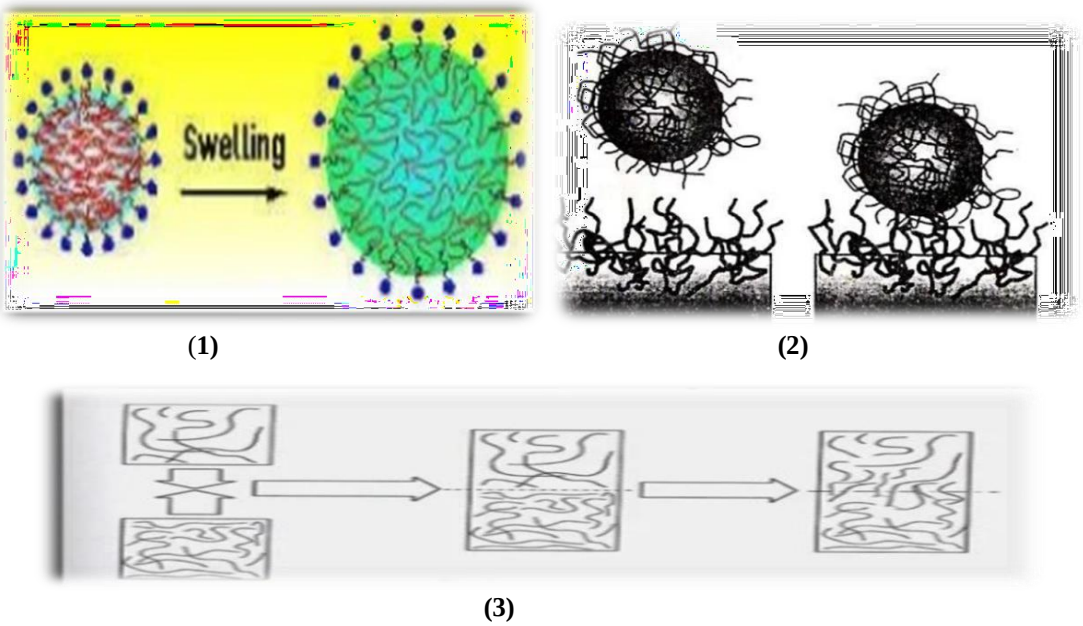


Buccal dosage forms:

1. Buccal mucoadhesive tablets.
2. Patches and films.
3. Semi-solid preparations (ointments and gels)
4. Powders.

Mechanism of Mucoadhesion [3-6]

- Muco adhesion is the process of a medicine and an appropriate carrier adhering to the mucous membrane. Muco adhesion is a multi-step process that includes
- Wetting
- Adsorption
- Polymer chain interpenetration.
- Intimate contact between a bioadhesive and a membrane, caused by the bioadhesive swelling or by a good wetting of the bio adhesive and the membrane. (The occurrence of wetness or swelling).
- The bio adhesive's penetration into the tissue or the mucous membrane's surface. (Interpenetration).
- Enlargement of the sticky material and chemical connections due to electrostatic interaction, hydrophobic interactions, hydrogen bonding, and dispersion forces are the most common physical and chemical interactions that occur between the mucus and thebiological substance. (Chemical Bonding).

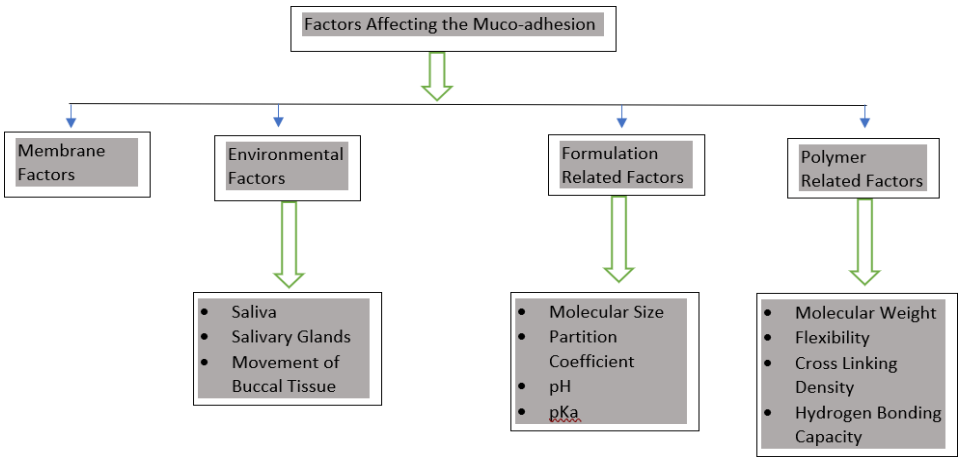


(1) **(2)**

(3)

Fig 1.2: (1) Wetting & Swelling (2) Interpenetration (3) Chemical Bonding

FACTORS AFFECTING MUCO-ADHESION[7-10]



1. **Membrane Factors:** The degree of keratinization, the surface area of absorption, the mucus layer of the salivary pellicle, epithelial intercellular lipids, the basement membrane, and the lamina propria can all affect buccal absorption.
   The thickness of the absorptive membrane, blood supply/lymph drainage, cell renewal, and enzyme content all have a role in lowering the rate and amount of medication that reaches the systemic circulation.

2. **Environmental Factors**:
   - **Saliva:** Salivary pellicle or film is a thin film of saliva that coats the buccal mucosa throughout the lining. Salivary film thickness ranges from 0.07 to 0.10 mm. The rate of buccal absorption is affected by the thickness, content, and mobility of this film.
   - **Salivary glands:** The salivary glands are found in the buccal mucosa's epithelium or deep epithelial area. Salivary glands regularly release mucus on the surface of the buccal mucosa. Mucus aids in the retention of mucoadhesive dose forms, but it can also act as a barrier to medication penetration.
   - **Movement of buccal tissues:** The buccal area of the oral cavity shows less vigorous motions. The mucoadhesive polymers are added in the dosage form to keep it in the buccal region for long periods of time, allowing it to withstand tissue movements while talking and, if possible, eating or swallowing.

3. **Formulation related factors**:
   - **Molecular size:** Molecules having smaller size (75-100 Da). With the increase of molecular size of drug the permeability decreases. For hydrophilic macromolecules like peptides, absorption enhancers have been utilised to successfully change the buccal epithelial permeability, making this route more suited for delivery of bigger molecules.
   - **Partition coefficient:** For determining the absorption potential of a drug partition coefficient is very useful tool. In general, boosting a drug's polarity through ionisation or adding hydroxyl, carboxyl, or amino groups increases its water solubility, which lowers the lipid water partition coefficient. Adding methyl or methylene groups to a medication decreases its polarity, resulting in an increased partition coefficient and decreased water solubility.
   - **pH:** The partition coefficient is also affected by the pH at the site of medication absorption. Acidic medications' partition coefficient drops as pH rises, whereas basic drugs' partition coefficient rises. Large amounts of lipid-soluble drugs are stored in fat storage in obese people. These medicines are dissolved in lipid and are stored in fat deposits as a reservoir for gradual release.
   - **pka:** The ionisation of a medication is intimately related to its pKa and pH at the mucosal surface. Many weak acids and weak bases have a high lipid solubility in their nonionized state, indicating that they can traverse lipoidal membranes**.** As a result, at the pH where the drug is unionized, maximum absorption is shown to occur. As the ionization of the drug increases, absorption decreases.

4. Polymer Related Factors:

- **Molecular weight:** When a polymer's molecular weight exceeds 100,000, its mucoadhesive strength increases. The molecular weights of polyoxyethylene polymers and their mucoadhesive strengths have a direct correlation of 200.000-7,000,000.
- **Flexibility:** The diffusion of polymer chains in the interfacial region is the first step in muco-adhesion. As a result, in order to produce the necessary entanglement with the miles, the polymer chain must have a significant degree of flexibility. The higher chain interpenetration was attributed to the polymer up operation of polyethylene glycol's greater structural flexibility. In general, the viscosities and diffusion coefficients of polymers can be used to determine their mobility and flexibility, as more flexibility of a polymer induces greater diffusion into the mucus network.
- **Cross-linking Density:** Three significant and interrelated structural factors of a polymer network are the average pore size, the quantity and average molecular weight of cross-linked polymers, and the density of cross-linking. As a result, it is plausible to assume that as the density of cross-linking increases, water diffusion into the polymer network slows, resulting in insufficient swelling of the polymer and a slower rate of interpenetration between polymer and mucin.
- **Hydrogen Bonding Capacity:** Another crucial aspect in a polymer's muco- adhesion is hydrogen bonding. To boost hydrogen bonding potential, desired polymers must include functional groups that may create hydrogen bonds. Polymer flexibility is also significant. Polymers with high hydrogen bonding capacity include poly (vinyl alcohol), hydroxylate methacrylate, and poly (methacrylic acid), as well as all of their copolymers.
- **Hydration:** Hydration is essential for a mucoadhesive polymer to expand and form a suitable macromolecular mes of sufficient size, as well as to induce mobility in the polymer chains to improve the interpenetration process between the polymer and the mucin. By exposing the bio-adhesive sites for hydrogen bonding and/or electrostatic contact between the polymer and the mucus network, polymer swelling allows mechanical entanglement. However, optimal swelling and muco-adhesion require a certain level of hydration of the muco- adhesive polymer.

- **Concentration:** The importance of this element can be explained by the polymer chain length available for penetration into the mucus layer, which is important for the creation of a strong adhesive connection with the mucus. When the polymer concentration is too low, the number of penetrating polymer chains per unit volume of mucus is minimal, and the polymer-mucus interaction is unstable. The more concentrated polymer would have a longer penetrating chain length and higher adherence in general. However, there is a critical concentration for each polymer at which it forms a "unperturbed" state due to its considerably coiled structure. As a result, the solvent's accessibility to the polymer reduces, and the polymer's chain penetration drops dramatically. As a result, increased polymer concentrations do not always improve and, in some situations, substantially worsen mucoadhesive characteristics. High concentrations of flexible polymeric films based on polyvinyl pyrrolidone or poly (vinyl alcohol) as film-forming polymers did not improve the polymer's mucoadhesive qualities, according to one of the research addressing this aspect.

Theories of Mucoadhesion [11-14]

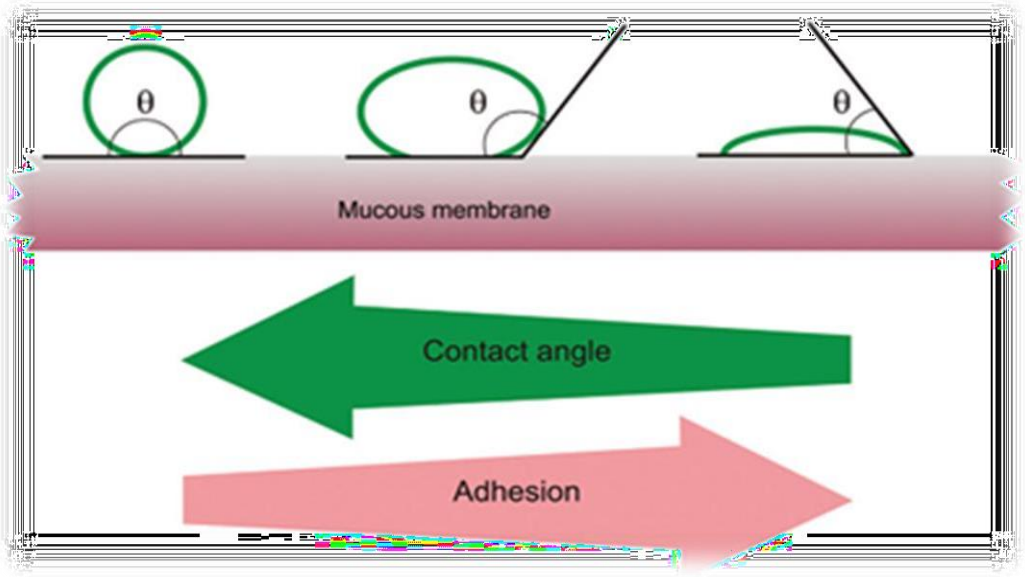
- **Wetting Theory:** The wetting theory refers to a liquid system that has an attraction for a surface and spreads over it. The contact angle/touch angle, for example, can be used to determine this affinity. The lower the contact angle, the greater the affinity, according to the usual norm. To offer enough spread ability, the contact angle should be equal to or close to zero.
  The difference between the surface and interfacial energies can be used to compute the spreadability coefficient (SAB), as indicated in the equation:

  SAB = $Y_B - Y_A - Y_{AB}$---------- 1.1)

  Where,
  Y_B, Y_A = Surface Energies
  Y_{AB}= Interfacial Energy

  If interfacial energy is greater than individual surface energy, then adhesion work (W_A) will be greater, i.e greater energy required to separate the two phases.

  $W_A = Y_A + Y_B - Y_{AB}$---------- (1.2)



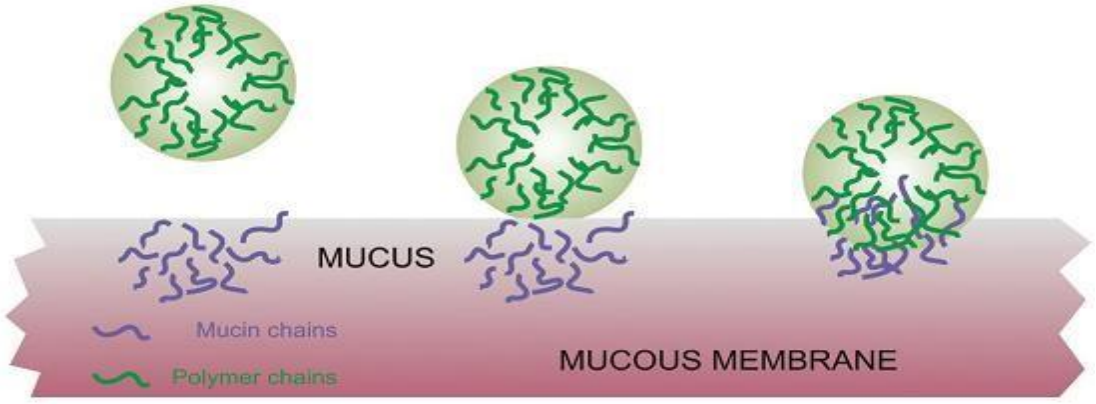
Influence of Contact angle on Mucoadhesion

- **Diffusion Theory:** Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to form a semi-permanent adhesive bond. According to this theory, a semi-permanent adhesive bond is formed when polymer chains and mucus combine to a certain depth. The diffusion coefficient, flexibility and composition of the mucoadhesive chains, motility, and contact time all influence how deep the polymer chains penetrate the mucus. The value of molecular weight between cross links determines the diffusion coefficient. The diffusion coefficient reduces dramatically as the cross-linking density decreases. To generate a successful bio-adhesive bond, the depths of mucus penetration should be in the range of 02-0.5 m, according to the literature. This polymer interpenetration depth and mucin chains can be determined by the following equation:

$$I = (t\ Db)^{1/2}$$

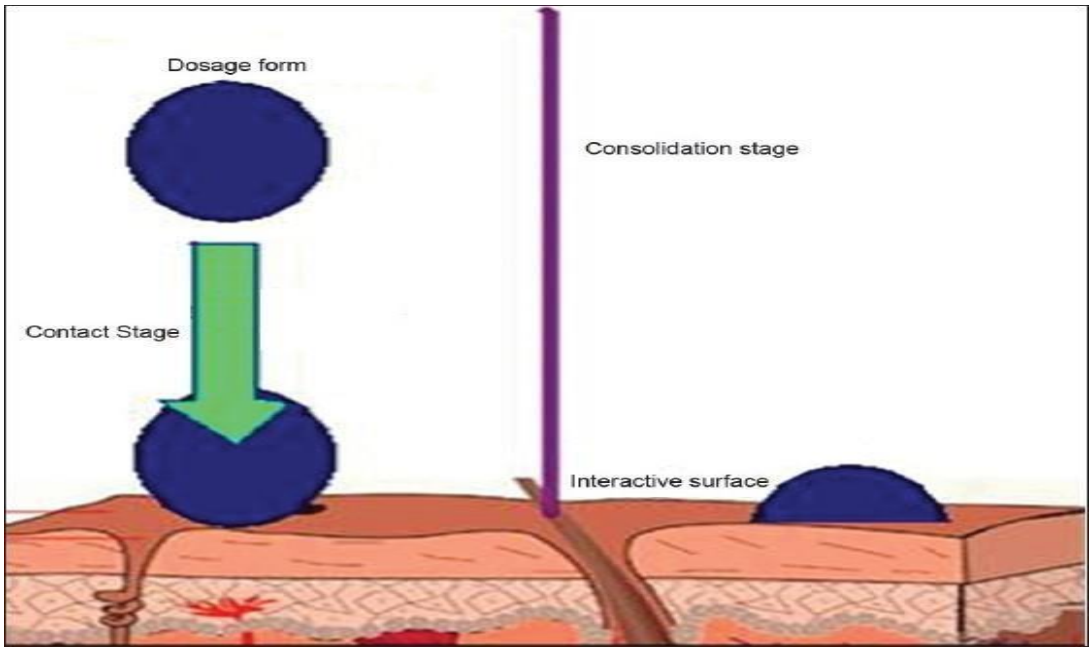
Where, **t** = Contact Time
Db = Diffusion coefficient of the mucoadhesive material in the mucus

It is critical for diffusion to occur that both the bio-adhesive and mucus components involved have adequate mutual solubility, i.e., chemical structures that are comparable. The stronger the mucoadhesive connection, the higher the structural similarity.



Interaction Between Polymer Chain of Mucoadhesive Device and Mucous

- **Adsorption Theory:** Kembell and Hantsherger described the adsorption theory. Adhesion, according to this idea, is caused by numerous surface interactions between the sticky polymer and the mucous substrate. Ionic, covalent, and metallic bonding result in adhesion as a result of primary chemisorption, which is generally undesired due to their persistence. Vander Waals forces, hydrophobic contact, and hydrogen bonding are the main causes of secondary bonds. According to this idea, the mucin is wet at first, and then the polymer diffuses into the mucin layer, causing the layers to fracture, resulting in adhesion, electronic transfer, or simple adsorption, and eventuallytotal muco-adhesion.



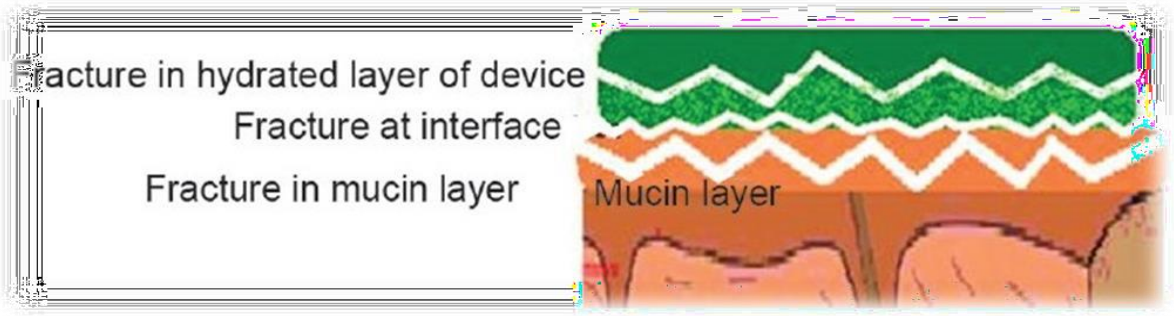
Process of Consolidation

- **Electronic Theory:** Derjaguin and Smigla proposed the electrical theory of adhesion. The electrical theory is based on the assumption that the surface characteristics of the bioadhesive material and the biological material to be adhered to differ. According to this theory, electron transfer occurs when two surfaces come into contact in an attempt to equalise Fermi levels, resulting in the formation of a double layer of electrical charge at the bioadhesive and biologic surfaces. The bioadhesive force is hypothesised to be caused by attractive forces across this second layer.

- **Fracture Theory:** According to this idea, the force required to separate both surfaces is proportional to the system's adhesive bond. The force required to separate the polymer from the mucosa is related to the strength of their binding in this "fracture theory." The work fracture will be higher the longer the polymer network strands are. Alternatively, if the degree of cross-linking within a system is reduced, the work fracture will rise. This can be determined by the following equation:

$$r = (E \times e / L)^{1/2}$$

Where, r = Fracture Strength
e = Fracture Energy
E = Young's Modulus of Elasticity
L = The Critical Crack Length



Fracture Occur ring for Muco-adhesion

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