

A Review On Mucoadhesive Buccal Dosage Form

Mr. Soham.S. Jadhav*¹, Miss. Shruti.S. Jadhav*², Miss.Vaishnavi.A. Jadhav*³

Miss.Rachana.S.Das*⁴

*1,2,3 Students , Department of Pharmaceutics , JBVPS Vidya Niketan College of Pharmacy
Lakhewadi , India

*4 Assistant Professor , Department of Pharmaceutics , JBVPS Vidya Niketan College of Pharmacy
Lakhewadi , India

ABSTRACT:

Mucoadhesive drug delivery methods extend the dosage form's residence duration at the site of absorption by interacting with mucous molecules and the mucus layer that covers the mucosal epithelial surface. The buccal area of the oral cavity is a desirable site for the drug of choice's delivery, especially when it comes to addressing the drawbacks of the latter route. By using the buccal route to provide the medication, issues such high first-pass metabolism and drug degradation in the gastrointestinal environment can be avoided. Some specific patients, primarily paediatric and geriatric patients, have benefited from mucoadhesive drug delivery system. Several difficulties, including target delivery, dosage form spitting, dose estimation, flavour masking when creating a delivery method for these particular patient populations, challenges include toxicity, adverse medication reactions, and the Medicine Bioavailability. Drugs can also be given to patients who are unconscious and uncooperative. Adhesive mucosal dosage forms, such as adhesive tablets, adhesive gels, adhesive patches, and numerous more dosage forms, were recommended for oral administration in order to prevent unintentional medication swallowing.

KEYWORDS : Bio adhesion Polymer, Oral mucosa , Dosage form,

INTRODUCTION:

The patient prefers the oral route over all other dosing forms. Certain kinds of medications, such as proteins and peptides, cannot be administered orally due to the drawbacks of hepatic first pass metabolism and GI tract enzymatic breakdown ¹ The bond created when a pressure-sensitive adhesive comes into contact with a surface is known as adhesion. According to the American Society of Testing and Materials, It is the state in which two surfaces are held together by interfacial forces, which may comprise valence forces, interlocking action, or both. Mucoadhesive drug delivery methods prolong the residence period of the dose form at the site of application or Absorption They enhance the drug's therapeutic efficacy by facilitating close contact between the dosage form and the underlying absorption surface. For both systemic and local effects, numerous mucoadhesive drug delivery systems have been developed recently for oral, buccal, nasal, rectal, and vaginal routes.² Pharmaceutical technology has shown a lot of interest in polymers. Mucoadhesive polymers are now recognized as a key tactic for extending the residence period and enhancing the localized effects of drug delivery methods on different biological systems' mucous membranes.³

Mucoadhesive dose forms have also been used for rectal and vaginal drug delivery. These methods have a number of benefits, including the avoidance of pain, tissue damage, first pass metabolism, and the reduction of hepatic adverse effects, which are frequently observed with parenteral administration. Gelatine, mucin, poloxamer, and polycarbophil are the polymers utilized for rectal and vaginal medication delivery. Creams, ointments, Emulex in-situ gels, and pills are some of the rectal and vaginal formulations.

⁴ In recent years, there has been a lot of interest in the pharmaceutical aspects of mucoadhesion because it offers the potential to prevent either hepatic first-pass inactivation of the drug or destruction by gastrointestinal contents. The following are components of the mucoadhesive drug delivery system:

1. Systems for buccal medication delivery
2. Sublingual medication administration methods
3. Systems for rectal medication delivery
4. Drug delivery techniques via the vagina
5. Drug delivery systems for the eyes
6. Nasal medication delivery devices

One of the natural polymers that is frequently utilized is chitosan. Glucosamine and N-acetyl glucosamine, which are also components of mammalian tissue, make up chitosan. It is a biodegradable, biocompatible, and nontoxic polymer. This polymer is taken into consideration because of its capacity to create both films and matrices ⁵ The goal of releasing the medication gradually over an extended length of time can be accomplished by the development of sustain release dosage forms, but this is insufficient to deliver a long-lasting therapeutic impact. Before the drug content is emptied, they might be removed from the site of absorption. Rather, the mucoadhesive dosage form will fulfil the functions of both sustained release and dosage form presence at the absorption site. In this sense, a few elements of mucoadhesive drug delivery systems are highlighted in our review ⁶

ADVANTAGES:

1. The drug is simple to administer, and it is possible to stop therapy in an emergency.
2. Extended duration of drug release.
3. Drugs can be given to traumatized and unconscious patients.
4. Drugs boost bioavailability by avoiding the first pass metabolism.
5. Buccal administration is an option for certain medications that are unstable in the stomach's acidic environment.
6. The passive diffusion method of drug absorption.
7. Adaptability in terms of surface, size, shape, and physical state.
8. Close contact with the absorbing membrane results in a maximum absorption rate.
9. Rapid initial action ⁷

LIMITATION:

- 1.It is not possible to deliver medications that are unstable at buccal pH.
2. Substances with an unpleasant or bitter taste or This method cannot be used to deliver medication that has an unpleasant smell or irritates the mucosa.
- 3.Drug required with small dose can only be administered.
- 4.Only this method can be used to give medications that are absorbed through passive diffusion.
- 5.Eating and drinking may restrict⁸

THE ANATOMY AND PHYSIOLOGY OF THE ORAL MUCOSA:

The mouth cavity has a total surface area of 100 cm² and is covered in mucous membranes. Additional sections include the palatal mucosa, the gums (gingiva), the floor of the mouth (sublingual), the buccal mucosa (cheeks), and the lining of the lips. A multilayered epithelium encased in mucus makes up the oral mucosal tissues. The lamina propria, a layer of connective tissue, is joined to the epithelium by the basal lamina. The oral mucosa shields the body from outside factors like potentially harmful substances entering the body. The human oral mucosa's epithelium exhibits a number of unique maturation patterns that are connected to the tissue's functional requirements. The less flexible masticatory mucosa of the gingiva and a portion of the hard palate include keratinized epithelium, which is dried, mechanically tough, and chemically resistant. The surface of the mucosa that lines the soft palate, floor of the mouth, lips, and cheeks is made of flexible, non-keratinized epithelium. The distinct epithelium of the buccal mucosal tissue is multilayered⁹

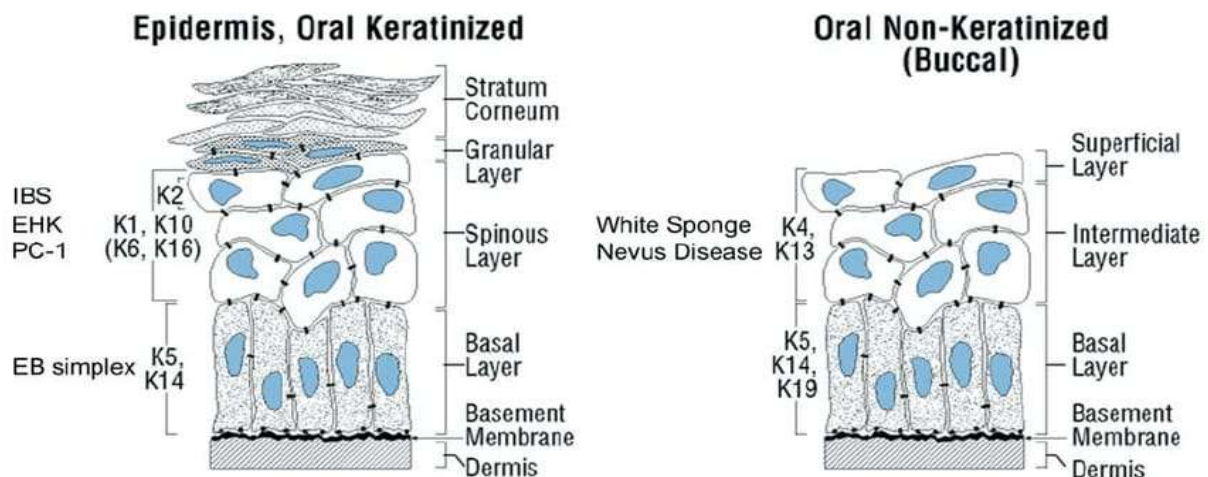


figure.1 oral keratinized epithelium and non-keratinized epithelium

MECHANISM OF MUCOADHESION:

Mucoadhesion is an Interfacial Phenomena when two materials are kept together by interfacial forces of attraction. One of the materials may be artificial, such as mucoadhesive polymer, and the other may be the mucin layer of mucosal tissue. An artificial material that interacts with mucous membranes and can stay on them or hold them together for a long time is referred to as “mucoadhesive.” The two steps that have typically been identified during the adhesion process are listed below

The latter have or are close to tissues that have specialized glands like salivary glands that produce mucus onto the epithelial surface, whereas the former have goblet cells that secrete mucus directly onto the epithelial surfaces. Mucus can be found as a luminal soluble or suspended state or as a gel layer that adheres to the mucosal surface. Mucin glycoproteins, lipids, inorganic salts, and water—which makes up over 95% of their weight—are the main constituents of all mucus gels, making them a highly hydrated system. Mucus has two main purposes: lubrication and protection. An artificial material that interacts with mucous membranes and can stay on them or hold them together for a long time is referred to as mucoadhesive. Below are the two phases that have often been shown to occur during the adhesion process^{10,11}

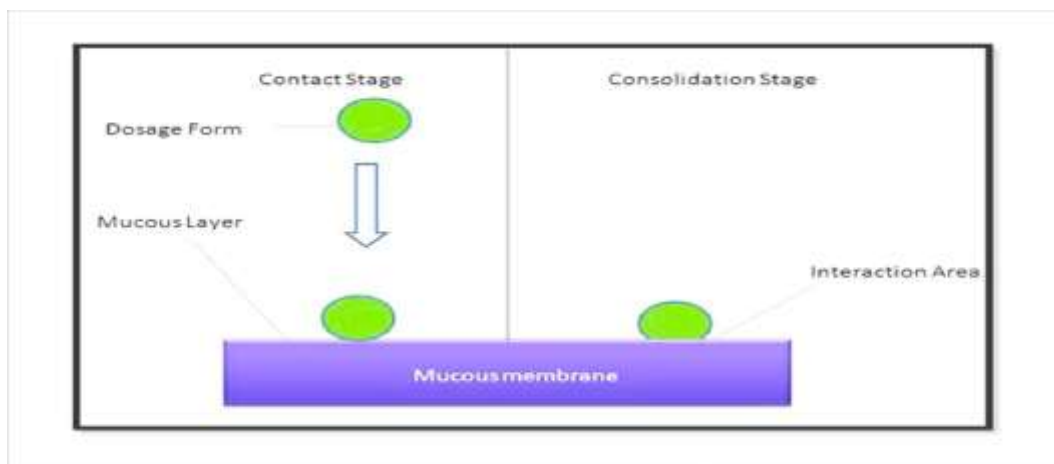


figure.2 mechanism of mucoadhesion

CONTACT STAGE:

The contact stage represents the initial phase of mucoadhesion, during which the mucoadhesive polymer comes into close proximity and establishes physical contact with the mucosal surface. Wetting and spreading of the dosage form over the mucosa are critical events in this phase. Hydration of the polymer begins upon exposure to mucosal fluids, allowing polymer chains to loosen, swell and gain mobility. This facilitates improved surface contact and partial penetration of the polymer into minute surface irregularities of the mucus layer. The efficiency of the contact stage depends largely on the polymer rheological behaviour surface energy, wetting properties and the presence of mechanical pressure during application. Proper contact is essential because it determines how effectively the subsequent adhesive interactions can form during the next stage¹²

CONSOLIDATION STAGE:

The consolidation stage involves the strengthening of the initial contact through various molecular interactions between the polymer chains and the mucin glycoproteins. Once hydration is complete, the polymer swells sufficiently to allow interpenetration of polymer chains with mucin chains. This chain entanglement forms a cohesive and stable adhesive bond. Physicochemical forces such as hydrogen bonding, electrostatic interactions, van der Waals forces and hydrophobic interactions contribute further to consolidation. The strength of this stage is influenced by polymer molecular weight, flexibility, cross-linking density, degree of hydration and the physicochemical environment of the mucosa. A greater degree

of polymer–mucin interpenetration and bonding leads to stronger mucoadhesion and prolonged residence time at the application site. ¹³

table no.1 role of polymer in drug release

Sr. No.	Drug	Polymer	Role
1.	Ondansetron	Carbopol, sodium alginate gelatine.	Rapid absorption through buccal mucosa.
2.	Domperidone	Taro gum, Carbopol 934P, HPMC	Improve bioavailability and retention.
3.	Nicotine	Carbomer alginic acid sodium salt, HPMC	Controlled drug delivery system.
4.	Metronidazole	Carbopol 934P, HPMC, sodium carvomenthol cellulose	Enhance adhesive controlled release.
5.	Nifedipine	Acacia, chitosan, HPMC	Enhance adhesive permeability
6.	Ibuprofen	Carbopol ,934P, HPMC, PVP, K30.	Enhance sustained release.
7.	Diltiazem	Chitosan, sodium alginate.	Improve residence time provide strong melodeon-controlled release.
8.	Diphenhydramine HCL	HPMC, Carbopol, 971P,	Prolonged release better bioavailability.
9.	Propranolol HCL	Carbopol, sodium alginate ,934P	Control release cohesion.
10.	Lidocaine	Carbopol 934P, sodium alginate.	Local anaesthetic buccal delivery.

MUCOADHESION THEORIES:

Many theories have been put up to explain the mechanics underlying the complicated process of cohesion. Mechanical interlocking, electrostatic, diffusion interpenetration, adsorption, and fracture processes are some of these hypotheses

ELECTRONIC THEORY: The electronic theory states that mucin surfaces and bio adhesion systems have different electronic structures, which leads to the creation of an electronic gradient. When these two systems—

the mucin surface and the bio adhesive system—come into contact with one another, electrons are transferred because of this difference in electrical structure. An electronic bi-layer forms at the interface between the two surfaces as a result of this electron transport. An effective mucoadhesion may result from this interfacial bi-layer's attractive force at the interface of two surfaces ¹⁴

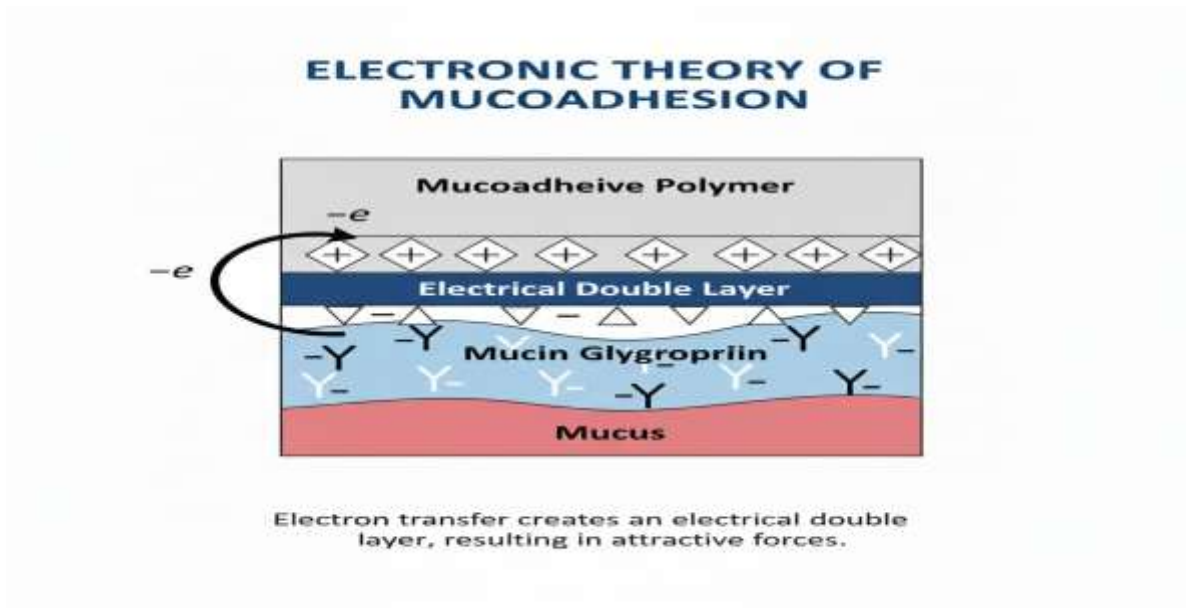


figure.3 electronic theory

ADSORPTION THEORY: This theory states that the substance clings to two surfaces after an initial contact due of surface forces between the atoms in the two surfaces. These pressures can produce two distinct kinds of chemical bonding.

(i) Covalent primary chemical bonds, which are unfavourable in mucoadhesion due to the possibility of permanent bonding due to their great strength.¹⁵

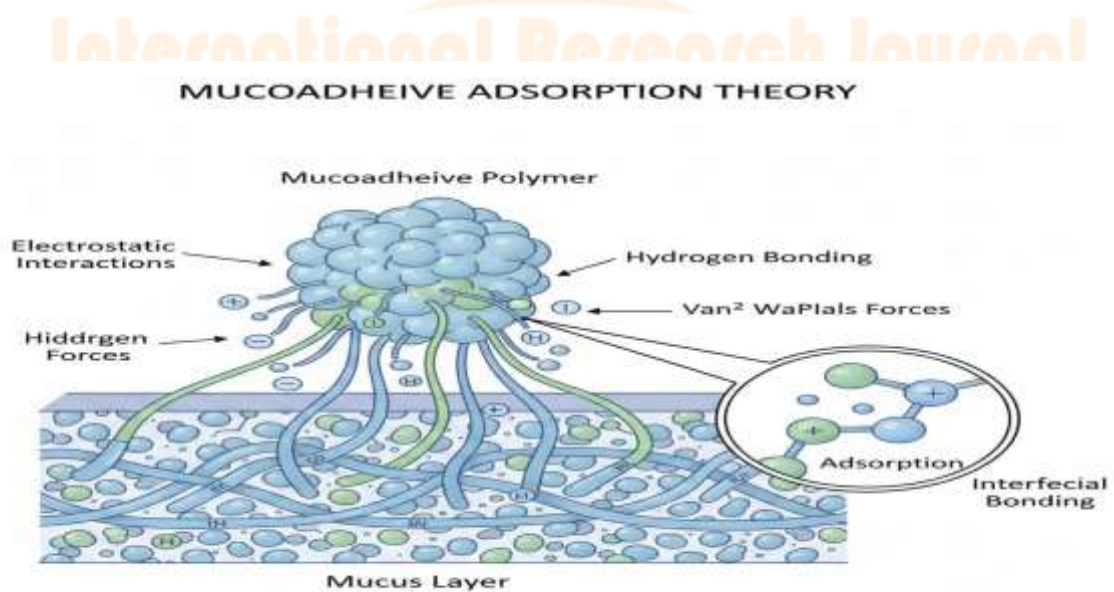


figure .4 adsorption theory

WETTING THEORY: Low viscosity bio adhesives and liquid systems are covered by the wetting theory. In order to spread over it, it explains the affinity for the surface. A key factor in predicting mucoadhesive

performance is the surface energy of the polymer and tissue. According to this notion, the affinity increases with decreasing contact angle. For appropriate velocity, the contact angle must be equal to or near zero. As stated in the following equation, the Spread ability coefficient, or SAB, can be computed by subtracting the interfacial energy (γ_{SL}) from the surface energies (γ_{SG} and γ_{LG}). In order to attain a high degree of mucoadhesion, this theory emphasizes the significance of contact angle and the decrease of surface and interfacial energy. S is equal to γ_{SG} minus $(\gamma_{SL} \text{ minus } \gamma_{LG})$.¹⁶

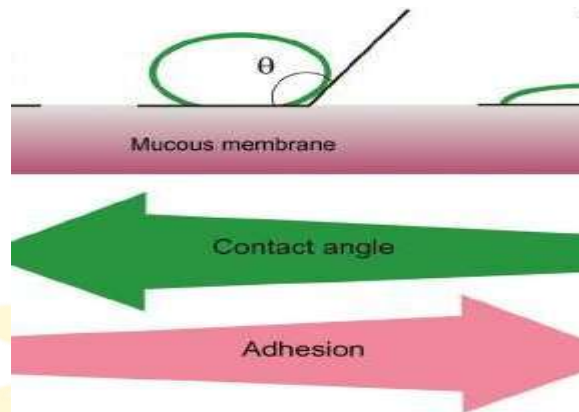


figure.5 wetting theory

DIFFUSION THEORY:

The hypothesis of diffusion Interlocking According to this theory, the polymeric chain of the drug delivery system and the polymeric chain of the mucous membrane—that is, glycol proteins—are mechanically bonded. The polymeric chain of the drug delivery system enters the glycoprotein network when two surfaces come into close contact. This theory states that the diffusion coefficient of both polymeric chains essentially determines the bio adhesion. Molecular weight, cross-linking density, chain flexibility, and temperature are other variables that could affect the polymeric chain's mobility. Effective mucoadhesion requires the bio adhesive medium to be similarly soluble to glycoprotein¹⁷

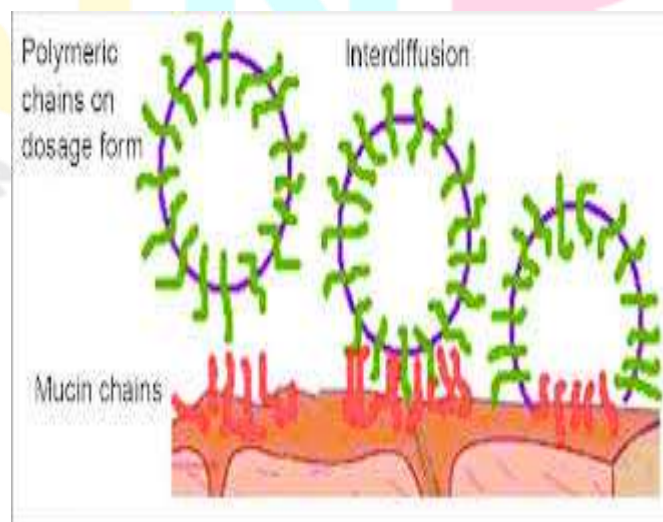


figure.6 diffusion theory

FRACTURE THEORY: The most well acknowledged theory on mucoadhesion is fracture theory. The force needed to separate two surfaces following adhesion is examined by this hypothesis. It can be expressed using the formula below and measures the highest tensile strength during detachment.

$$G = (E\varepsilon/L)^{1/2}$$

Where Young's modulus of elasticity, or E

ε : Fracture energy

When two surfaces are separated, L is the critical crack length.

G—Details of the fracture strength equation ¹⁸

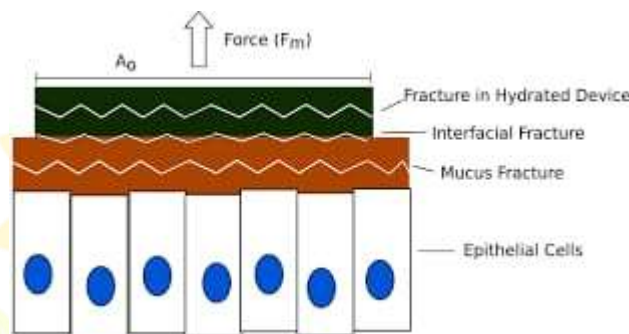


figure.7 fracture theory

DEHYDRATION THEORY: In aqueous environment while materials come in contact with mucus, it becomes jellified and water is added to the dosage form due to the gradient in concentration until the Osmotic Equilibrium is achieved. Consequently, the duration of contact between the formulation mixture and mucus on the mucosal membrane increases. Therefore, it is the movement of water, not the interpenetration of macromolecule chains that causes adhesive connections to strengthen

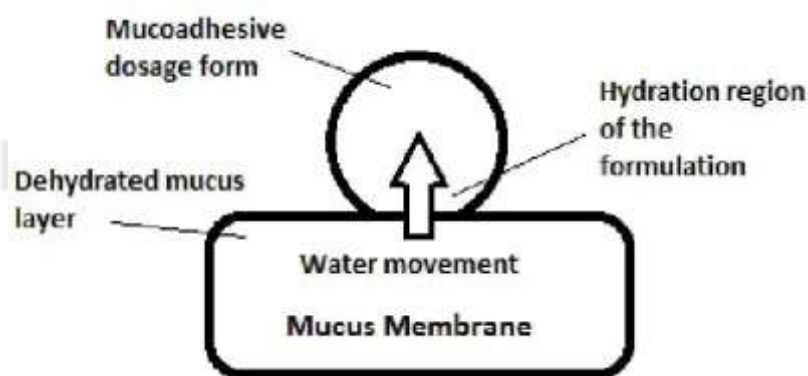


figure.8 dehydration theory

METHODS USED TO PREPARE MUCOADHESIVE BUCCAL TABLET:

DIRECT COMPRESSION:

The preparation of mucoadhesive buccal tablets is generally carried out using techniques such as direct compression, wet granulation, and melt granulation, selected based on the properties of the drug and polymers. In the direct compression method, the required quantities of drug, mucoadhesive polymer, and diluents are first sieved to obtain a uniform particle size and then blended to ensure homogeneous mixing. Lubricants such as magnesium stearate are added at the final stage to improve flow and prevent sticking. The blended powder is then compressed using a tablet press to obtain uniform buccal tablets, making this technique suitable for moisture- and heat-sensitive drugs³⁰.

WET GRANULATION METHOD:

Another widely used technique is the wet granulation method, which improves the flow behaviour and compressibility of powder mixtures. In this method, the drug and selected mucoadhesive polymers are initially blended, after which a binder solution—commonly containing PVP or HPMC—is added to convert the powder into moist, cohesive granules. These granules are dried at controlled temperatures, passed through a sieve to achieve uniform size, and finally mixed with lubricants before compression. Wet granulation provides better mechanical strength and uniformity, making it suitable for polymers that do not compress well in their dry state.³¹

MELT GRANULATION METHOD:

The melt granulation method is preferred when low-melting carriers are used to enhance mucoadhesion or modify drug release. Here, the drug and polymer mixture is combined with a molten or softened binder such as PEG or Glaciar allowing granulation without the use of water or solvents. After thorough mixing, the mass is cooled and screened to obtain granules of consistent size, which are later lubricated and compressed into tablets. This method avoids potential hydrolytic degradation and is beneficial for drugs that are unstable in aqueous environments. Overall, these techniques provide flexibility in formulating mucoadhesive buccal tablets with desired adhesion strength, mechanical integrity, and release characteristics.³²

FACTOR AFFECTING, MUCOADHESION:

The bio adhesive polymer and the surface it is present on determine the mucoadhesion qualities. The following is a summary of the variables that influence a polymer's mucoadhesive qualities.

MOLECULAR WEIGHT:

When a polymer's molecular weight exceeds 100,000, its mucoadhesive strength rises. The mucoadhesive strength of polyoxymethylene polymers is directly correlated with their molecular weights, which fall between 200,000 and 7,000,000.¹⁹

FLEXIBILITY:

Diffusion of polymer chains in the interfacial region is necessary for optimal bio adhesion. Therefore, in order to improve adhesion, the polymer chain must have a significant degree of flexibility. The viscosities and diffusion coefficients of polymers can be linked to their mobility and flexibility. A polymer's increased flexibility results in more diffusion into the mucus network.²²

POLYMER CONCENTRATION:

The ideal concentration of bio adhesive polymer is needed for maximum bio adhesion. Adhesive strength decreases in highly concentrated systems above the ideal level when coiled molecules separate from the medium. The number of penetrating polymer chains per unit volume of mucus is likewise low when the polymer concentration is too low. Concentrations between 1 and 2.5% may exhibit higher bio adhesion potential.²⁰

HYDROGEN BONDING CAPACITY:

Capacity to form hydrogen bonds Another crucial element in a polymer's mucoadhesion is hydrogen bonding. The flexibility of the polymer is crucial to enhancing the hydrogen bonding potential of desired polymers, which must include functional groups capable of forming hydrogen bonds. Polymers with strong hydrogen bonding capabilities include Poly vinyl alcohol, hydroxylated methacrylate, poly (methacrylic acid), and all of their copolymers.^{21,13}

CROSS LINKING DENSITY:

Three crucial and connected structural characteristics of a polymer network are the quantity and average molecular weight of the cross-linked polymers as well as the density of cross-linking. Consequently, it makes sense that as cross-linking density increases, water diffuses into the polymer network at a slower pace, which results in insufficient polymer swelling and a slower rate of polymer-mucin interpenetration.²¹

PH OF POLYMER:

pH of polymer-substrate interface: The polymer-mucin interface should have the same pH as much as feasible since the larger pH gradient between the two systems may trigger charge transfer. Mucoadhesion may be impacted by this.²³

EVALUTION OF BUCCAL MUCOADHESIVE DOSAGE FORM:**THICKNESS:**

Vernier calliper was used to measure the thickness of three randomly chosen tablets. Determine the tablets' average thickness.

WEIGHT VARIATION:

Each formulation of twenty tablets was chosen at random, and each tablet was weighed independently. Determine the pills' average mass.²⁴

DRUG CONTENT:

Each formulation contains 20 randomly chosen pills. Triturate tablets in a machine until they are a fine powder. fine powder (10 mg) was added to a 100 ml volumetric flask, the total volume was made up with pH 6.8 phosphate buffer, and the mixture was filtered. The drug content of each sample was tested using a UV-visible spectrometer at a maximum wavelength

TABLET HARDNESS:

Tablet hardness was measured in a lab using this method to determine how hard the tablets would be after handling and storage. Using a hardness tester such as the Monsanto hardness tester, we can determine the hardness of the tablets. Each batch of six tablets was crushed with a specified weight, which was recorded in kg/cm², and the average weight was computed.²⁵

SWELLING INDEX:

The swelling behaviour of a mucoadhesive dosage form is commonly assessed by determining its swelling index. In this method, the initial weight of the dry formulation is recorded, after which the sample is placed on a wire mesh or holder and immersed in simulated saliva or phosphate buffer (pH 6.8) maintained at 37 °C. At selected time intervals, the formulation is removed from the medium, carefully blotted with filter paper to eliminate excess surface fluid, and immediately weighed. This procedure may be repeated across several time points to obtain swelling kinetics. The degree of swelling is calculated using the formula:¹³

IN VITRO DRUG RELEASE :

With a few modest adjustments, USP II (rotating paddle) dissolution equipment (Elecrolab TDT 08L) was used for in vitro drug release investigations. 200 Millilitre of phosphate buffer (pH 6.8) with 2.5% polysorbate 80 made up the dissolving medium. The release investigation was conducted at a rotation speed of 25 rpm and a temperature of 37°C ± 0.5°C. Cyanoacrylate adhesive was used to secure the buccal tablet's backing layer to the glass disk. The disk was positioned near the dissolution vessel's bottom. At prearranged intervals, 5 ml samples were taken out and replaced with new medium. Following the proper dilution, the samples were filtered through 0.2-µm Whatman filter paper and examined at 307 nm using a UV spectrophotometer (Shimadzu, 1800). UV spectrophotometry (1601 Shimadzu) was used to quantify the medication.¹³

RHEOLOGICAL STUDY:

An appropriate in vitro model that correlates with the in vivo performance of a mucoadhesive polymer can be supplied by polymer-mucus mixture rheological data. Comparing binary mucus/polymer blends to similarly concentrated mono Component mucus/polymer systems is the most effective way to assess a polymer's mucoadhesive capability. The rheological behaviour of the two macromolecular species is

altered by chain interlocking, conformational changes, and chemical interactions between the bio adhesion polymer and mucin chains.²⁶

COLLOIDAL GOLD STAINING METHOD:

This novel in vitro technique was presented for comparing the mucoadhesive characteristics of different hydrogels. The adsorbed mucin-gold conjugates stabilize the red colloidal gold particles used in the procedure. The contact causes the mucoadhesive surface to turn red. Mucoadhesive qualities can be objectively compared by measuring the intensity of the red color.²⁷

FLUORESCENT PROBE METHOD:

When compared to the control cell, the polymer's ability to stick to this cell may result in a change Using pyrene as a fluorescent probe, the lipid bilayer of cultivated human conjunctiva cells is in fluorescence because of the possibility of surface compression. The amount of polymer binding directly correlates with this shift in fluorescence. Another probe can be used to measure the density on adhesion, polymer charge, and charge sign. It claims that the molecular interaction of the polymer with mucus is the basis for determining the bio adhesive bond.²⁸

FUTURE PROSPECTIVE:

Provides numerous benefits in terms of cost, accessibility, administration, withdrawal, and compliance among patients. The distribution of proteins, peptides, and vaccine formulations is where buccal adhesive drug delivery is headed. Better methods for creating buccal formulations to administer the medications in combination include bilayer buccal tablets, films, and patches. In order to increase the limited oral bioavailability of medications, scientists are developing buccal adhesive dose forms in a variety of ways. The second generation mucoadhesive polymer is discovered to have a lot of promise. There is now a novel buccal adhesive delivery system that directs medication distribution to the buccal mucosa while taking the oral site's local environment into account.²⁹

CONCLUSION:

The effective design of innovative mucoadhesive drug delivery systems may benefit from this summary of mucoadhesive dosage forms. Buccal medication delivery has several benefits. Over alternative forms of dosing. Therefore, the majority of research being done now focuses on creating new dosage forms to get over drawbacks. It allows for close contact between the dosage form and the buccal cavity, resulting in extended drug release. Given the large number of novel compounds resulting from pharmacological research, mucoadhesive systems could become more and more important in the creation of novel medications.

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Research Through Innovation