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The Mucoadhesive Buccal Drug Delivery System: A Review

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ABSTRACT

Mucoadhesion is a process of adhesion between the mucoadhesive drug delivery system and the mucus layer covering the mucosal epithelial surface. The mucus layer present on the mucosal surface serves as a physical barrier to protect the underlying tissues against external threats such as pathogens, toxins, and foreign particles. Therefore, the mucoadhesive drug delivery system interacts with the mucus layer and enhances the residence time of the dosage form at the site of absorption. This leads to increased drug plasma concentrations and therapeutic activity. Factors that influence the mucoadhesive properties of drug delivery systems include the physicochemical properties of the drug, the mucoadhesive polymer, and the mucus layer, pH, temperature, and ionic strength. The size and shape of the drug delivery system also play a crucial role in the mucoadhesive properties. Various mucoadhesive dosage forms have been developed, such as patches, tablets, films, microspheres, and nanoparticles. These dosage forms exhibit prolonged retention time and controlled drug release, leading to enhanced therapeutic efficacy. Mucoadhesive drug delivery systems have been used for the treatment of several local diseases like gastrointestinal disorders, ocular diseases, and vaginal infections. In conclusion, mucoadhesive drug delivery systems have proven to be advantageous in increasing drug plasma concentrations and therapeutic activity. The selection of mucoadhesive polymers, size, and shape of the drug delivery system, and the mechanism of adhesion are critical factors in developing a successful mucoadhesive drug delivery system.

INTRODUCTION [1-6]

The oral route is the one that patients most often choose among the several drug delivery methods. Many drugs cannot be effectively delivered via the traditional oral route based on our current knowledge of the biochemical and physiological aspects of absorption and metabolism. This is because these drugs are extensively subjected to pre-systemic clearance in the liver after administration, which frequently results in a lack of correlation between membrane permeability, absorption, and bioavailability. There are various different types of oral medication administration. Buccal drug delivery is a good alternative among the different routes of drug delivery because this route also has some drawbacks, such as hepatic first pass metabolism and enzymatic degradation within the GI tract, which prevent oral administration of certain classes of drugs, particularly peptides and proteins. The buccal area of the mouth mucosal cavity provides a desirable route of administration for systemic medication delivery. For systemic medication delivery, buccal methods of administration offer many benefits over other routes, such as bypassing the first pass effect and delivering drugs straight to the systemic circulation and avoiding pre-systemic clearance in the GI tract. These elements make the buccal location for systemic medication delivery very appealing and practical. When compared to other drug delivery methods that have limited patient compliance, such as rectal, vaginal, sublingual, and nasal drug delivery for controlled release, the buccal mucosa has a rich blood supply and is relatively permeable. The nasal cavity has been investigated by the research team as a potential site for systemic drug delivery, but the potential for irritation and the irreparable harm that chronic nasal dosage form application could cause to the ciliary action of the nasal cavity have forced this route to the back of the line for drug delivery. Rectal, vaginal, and ocular mucosae all have benefits, but due to the low patient tolerability of these locations, they are more often used for local applications than for systemic drug delivery. The buccal has considerable appeal for both local and systemic drug bioavailability due to its capacity to maintain a delivery system at a specific area for an extended length of time. Additionally, the route also provides quick drug transport to the systemic circulation and avoids degradation by stomach enzymes and first pass hepatic metabolism. The buccal mucosa are rich in blood supply and absorption occurs at this area is efficient. Also, the oral cavity is easily accessible for self-medication, and in the event of toxicity, the drug administration must be rapidly stopped by removing the dosage form from the buccal cavity. Because the buccal mucosa is less permeable than the sublingual location, it is a better option for extended medication administration.

Mucoadhesive Drug Delivery System in Oral Cavity [7-8]:

Drug delivery through the oral cavity's membranes can be split into the following categories:

1) Sublingual Delivery: Drugs are injected into the bloodstream through the mucosal membrane lining the bottom of the mouth.

2) Buccal Delivery: By inserting the drug between the gums and cheeks, medications are released through mucosal membrane into the systemic circulation.

3) Local Delivery: Medication is placed in the mouth. Buccal Bioadhesive Dosage Form Classification:

1. Buccal Bioadhesive Tablets.

2. Buccal Bioadhesive semisolids.

3. Buccal Bioadhesive patch and films.

4. Buccal Bioadhesive Powders.

1. Buccal Bioadhesive Tablets:

Dry dose forms known as buccal bioadhesive tablets must be moistened before being applied to the buccal mucosa. Bioadhesive polymers and excipients are already used in the formulation of double and multi-layered pills. These tablets are solid dosage forms that were made by directly compressing powder. Depending on the excipients included in the dosage form, they can be put in contact with the oral mucosa and allowed to adhere or dissolve. They have the ability to multi-directionally deliver drugs to the mucosal area or the oral cavity.

2. Buccal Bioadhesive Semisolids:

The finished powdered natural or synthetic polymers are then dispersed in polyethylene or an aqueous solution to create buccal bioadhesive semisolid dosage forms, such as are base.

3. Buccal Bioadhesive Patch and Films:

Buccal bioadhesive patches come in a round or oval shape and are constructed of multilayered thin films or two-ply laminates. They primarily have a bioadhesive polymeric layer and an impermeable backing layer that allow drugs to move unidirectionally across the

buccal mucosa. The drug is mixed with an alcohol solution of the bioadhesive polymer to create buccal bioadhesive sheets.

4. Buccal Bioadhesive Powders:

The buccal bioadhesive powder dose forms for Nifedipine are sprayed onto the buccal mucosa and contain a combination of bioadhesive polymers and the medication to reduce diastolic blood pressure.

Merits of Mucoadhesive Buccal Drug Administration [9-10-11]

1. It has a rich blood supply and a comparatively larger surface area.

2. It avoids the first-pass liver metabolism, increasing bioavailability.

3. The dosage form is simple to use, and in an emergency, prompt therapy termination can be eased.

4. An alternative method of giving drugs to people who are unconscious.

5. Increased patient adherence.

6. The quick start-up and prolonged drug delivery.

7. The buccal route is a superior delivery method for medications that cannot be administered through the stomach's acidic environment or that are susceptible to enzymatic degradation.

8. Passive diffusion does not require any stimulation for drug absorption.

9. Because the buccal mucosa is heavily vascularized, it is more permeable than skin.

Limitation of Mucoadhesive Buccal Drug Administration [4-9-11-12]

1. Large doses of medication cannot be given via this method.

2. It is difficult to administer medications that are not buccal pH stable.

3. Limits how much you consume and drink.

4. The prospect of the patient ingesting the formulation.

5. Drugs that induce mucosal irritation, have an unpleasant odour or taste, or both, cannot be administered via this route.

6. There is a finite amount of surface area for absorption.

7. Medication that is absorbed through diffusion must be given.

8. The medicine disintegrates with continuous salivation (0.5-2 L/Day).

Mucus Membranes:

The wet surfaces lining the walls of different bodily cavities, including the gastrointestinal and respiratory passages, are known as mucus membranes (mucosae). They are made up of a connective tissue layer called the lamina propria, which is followed by an epithelial layer whose surface is typically kept wet by a mucus layer. The stomach, small and large intestines, and bronchi are examples of epithelia that are either single stacked or multi-layered/stratified. The latter contain, or are close to tissues having, specialised glands like salivary glands that secrete mucus onto the epithelial surface. The former contains goblet cells, which are present in the former, immediately secrete mucus onto the epithelial surfaces. There is either a luminal soluble or suspended form of mucus or a gel layer of mucus that adheres to the mucosal surface. All mucus gels are primarily composed of mucin glycoproteins, lipids, inorganic ions, and water, which accounts for more than 95% of their weight and gives them a highly hydrated structure.[13] The two primary functions of mucus are lubrication and defence.

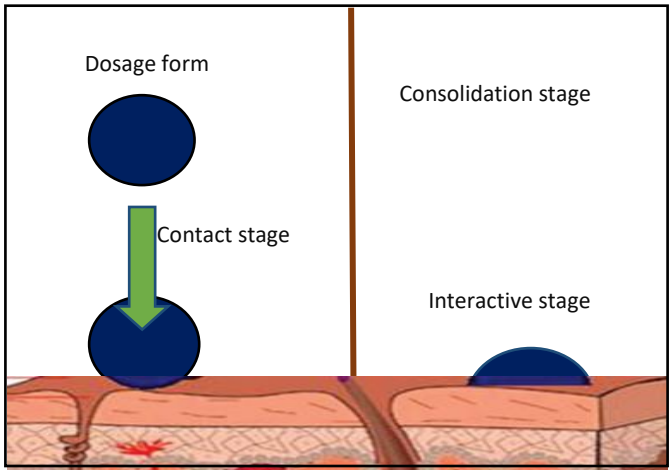

Figure No. 1: The Process of Contact & Consolidation

Basic components of buccal bioadhesive drug delivery system are:

1. Drug substance

2. Bioadhesive polymers

3. Backing membrane

4. Penetration enhancers

1. Drug Substance:

One must choose whether the intended action is for a local or systemic impact, and for a rapid or prolonged release before formulating mucoadhesive drug delivery systems. When choosing a drug for the design of buccoadhesive drug delivery systems, pharmacokinetic characteristics are crucial.

The medication needs to meet the requirements below: [14]

• The typical solitary dose of the medication should be extremely low.

• The biological half-lives of the drugs, which range from 2 to 8 hours, make them good options for controlled drug delivery.

• When a drug is taken orally, its T-max undergoes numerous shifts or increases in values.

• When given orally, a drug may show a first pass effect or pre-systemic drug elimination; however, passive drug absorption is preferred.

2. Bioadhesive Polymers:

The selection and characterization of suitable bioadhesive polymers for the formulation is the second stage in the creation of buccoadhesive dosage forms. In buccoadhesive drug delivery devices, bioadhesive polymers are crucial. An optimal polymer for buccoadhcsive drug delivery systems should have the properties listed below. Polymers are also used in matrix devices, where the drug is embedded in the polymer matrix, controlling the duration of release of drugs.

Characteristics.

• It ought to be environmentally friendly and inactive.

• It should adhere rapidly to moist tissue surface and have some site specificity.

• The polymer must not decompose during storage or the dosage form's shelf life.

• The polymer and its degradation products should be non-toxic and absorbable from the mucous layer.

• The polymer needs to be reasonably priced and readily accessible on the market.

3. Backing Membrane:

The backing membrane is crucial for the bioadhesive devices adhesion to the mucous membrane. The backing membrane's components ought to be impervious to penetration enhancers and medications. The buccal bioadhesive patches' impermeable membrane helps to ensure excellent patient cooperation while preventing drug loss. Magnesium stearate, HPC, polycarbophil, HPMC, CMC, carbopol, and other compounds are among those used in backing membranes.[16]

4. Penetration Enhancers:

They are included in the pharmaceutical formulation to speed up the membrane permeation rate of the co-administered medication. They increase the bioavailability of medications with poor membrane penetration without producing toxicity or membrane damage. The capacity to increase penetration depends on their use alone or in combination, the type of vehicle, the pharmacochemical properties of the drug.

Table No.1: Mucosal Penetration Enhancers and Mechanisms of Action [4-17-18-19-20-21-22]

Sr. No	Classification	Examples	Mechanism
1	**Surfactants**	**Anionic**: Sodium lauryl sulphate. **Cationic**: Cetylpyridinium chloride. **Nonionic**: Poloxamer, Briji, Span, Myrj, Tween. **Bile salt:** Sodium glycodeoxycholate, sodium glychocolate, Sodium taurodeoxycholate, Sodium taurocholate azone.	Perturbation of intercellular lipid, protein domain integrity.
2	**Fatty Acid**	Oleic acid, Ceprylic acid.	Increases fluidity of phospholipid domains.
3	**Cyclodextrines**	α, β, γ, cyclodextrine, methylated β-cyclodextrine	Inclusion of membrane compounds.
4	**Chelators**	EDTA, Sodium citrate.	Interfere with Ca polyacrylate.
5	**Positively Charged Polymers**	Chitosan, Trimethyl chitosan.	Ionic interaction with negative charge on the mucosal surface.
6	**Cationic Compound**	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface.

Mucoadhesion Theories:

Mucoadhesion is a complicated process, and many theories have been put forth to describe how it works. These ideas include fracture processes, electrostatic interlocking, diffusion interpenetration, and electrostatic interlocking.

Water hypothesis: The wetting theory is applicable to liquid systems that exhibit surface affinity and propagate across it. The contact angle is one measurement method that can be used to determine this attraction. According to the general norm, affinity increases with decreasing contact angle. For sufficient spreadability, the contact angle should be equal to or nearly equal to zero. The spreadability coefficient, SAB, can be calculated by subtracting the surface energies B and A from the interfacial energy AB, as shown in the expression below.[13] According to this theory, a sufficient amount of mucoadhesion depends on contact angle and the reduction of surface and interfacial energies.

$$SAB = \gamma B - \gamma A - \gamma AB$$

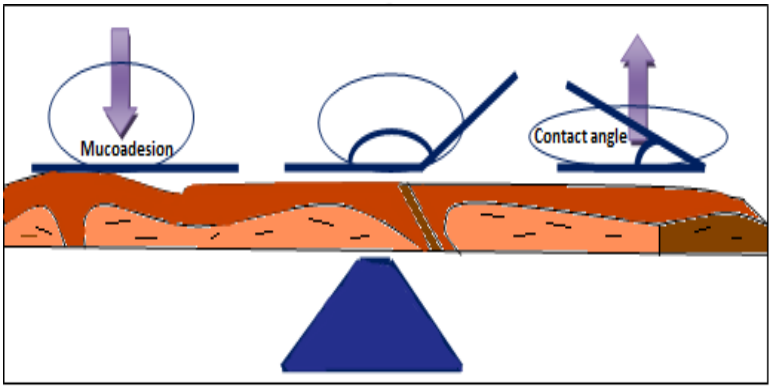

Figure No. 2: Influence of Contact Angle on Mucoadhesion

Diffusion Theory:

The interpenetration of polymer and mucin chains to a depth adequate to form a semi-permanent adhesive bond is described by diffusion theory. According to popular belief, the degree of polymer chain penetration has an impact on how strong the binding is. This penetration rate is influenced by the mucoadhesive chains' flexibility, nature, mobility, and contact time. It also relies on the diffusion coefficient. The literature states that a bioadhesive connection must form at a depth of interpenetration between 0.2 to 0.5 μm in order to be effective. The following equation can be used to determine the interpenetration depth of polymer and mucin chains:[13] l = (tDb) 12, where t is the contact time and Db is the

mucoadhesive material's mucus diffusion rate. When the depth of penetration is roughly equal to the polymer chain size, the adhesion strength of the polymer is achieved. It is critical for diffusion to occur when there is mutual solubility, which means that the mucus and the bioadhesive have similar chemical structures.[13]

Table No.2: Mucoadhesive polymers used in the oral cavity [4-19-26]

Criteria	Categories	Example
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

Fracture Theory:

In studies on the mechanical measurement of mucoadhesion, this hypothesis may be the one that is most frequently used. After adhesion has been proven, it examines the force necessary

to separate two surfaces. In tests of resistance to rupture, this force, sm, is commonly determined by the ratio of the maximum detachment force, Fm, and the total surface area, A0, involved in the adhesive interaction, where s F A m m = 0. The fracture theory does not consider the interpenetration or diffusion of polymer chains because it only considers the energy necessary to separate the parts. It is suitable for use in calculations for stiff or semi-rigid bioadhesive materials because they do not contain polymer chains that can pierce the mucus layer.[13,23]

The Electronic Theory:

According to this hypothesis, adhesion forms when electrons from the mucus and the mucoadhesive system transfer to one another due to differences in their electronic structures. At the mucus and mucoadhesive interface, a double layer of electrical charges is created as a consequence of the electron transfer between the two materials. The formation of attractive forces within this double layer is the end product of this process.[24]

The Adsorption Theory:

In this case, surface reactions (primary and secondary bonding) between the mucus substrate and the adhesive polymer lead to adhesion. Ionic, covalent, and metallic bonding from primary bonds caused by chemisorptions cause adhesion, which is typically unwanted due to their permanence.[25] Van der Waals forces, hydrophobic interactions, and hydrogen bonding are the primary causes of secondary bonds. These bonds have the benefit of being semi-permanent, so even though they take less energy to "break," they are the most common type of surface interaction in mucoadhesion processes.[26]

Instead of being viewed as distinct and opposing theories, each of these many theories should be seen as supplemental processes engaged in the various stages of the mucus/substrate interaction. Every hypothesis that attempts to explain the mucoadhesion process has equal weight. It is possible that the mucin will first be wetted, followed by the diffusion of the polymer into the mucin layer, which will break the layers and ultimately result in the ideal mucoadhesion through adhesion, electronic transfer, or simple adsorption. The nature of the mucus membrane and the mucoadhesive material, the type of formulation, the attachment procedure, and the subsequent environment of the bond will all affect the method by which a mucoadhesive bond is created. It is clear that a single mucoadhesion mechanism, as

suggested in many texts, is unlikely to account for all the various situations in which adhesion takes place.

Physiological Factors Affecting Buccal Bioavailability:

1. The epithelium's inherent permeability: The epithelium serves as a barrier with highly specialised absorption functions and is essential for permeability between the epidermis epithelium. In the oral region, the sublingual mucosa is more permeable than the buccal mucosa.

2. Epithelium breadth: The breadth of the buccal mucosa is between 500 to 800 μm. And this thickness changes at various locations within the oral cavity.

3. Blood supply: The existence of a lymphatic network in the lamina propria and a rich blood supply allows the drug molecules to be absorbed in the systemic circulation. The buccal mucosa has a blood flow rate of 2.4 ml per centimetre.

4. Metabolic activity: Because the drug is delivered straight to the blood, the first pass metabolism of the drug at the liver and gut wall is avoided. This method is used to transport drugs that are enzymatically labile, like proteins and peptides.

5. Saliva and mucus: The oral mucosa is continuously washed by the 0.5-2L of saliva that is secreted daily by the salivary duct. Due to the large amount of saliva present in the sublingual region, which speeds up drug absorption, bioavailability rises.

6. Ability to keep delivery system: Due to its smoothness and relative immobility, the buccal mucosa is used as a retentive drug delivery system.

7. Transport processes and routes: There are two ways for drugs to pass through the epithelia barrier:

• The paracellular pathway: passing between neighbouring epithelium cells.

• The transcellular pathway involves drug delivery across epithelial cells using mechanisms like passive diffusion, carrier-mediated transport, and endocytic processes.

Mucoadhesive Dosage Forms Tablets:

Tablets:

Tablets have a diameter of about 5-8 millimetres and are tiny, flat, and oval.[27] Mucoadhesive tablets, in contrast to traditional tablets, enable for speaking and drinking without any significant discomfort. They become softer, stick to the mucosa, and remain there until the dissolution or discharge is finished. Generally speaking, mucoadhesive tablets have the potential to be used for controlled release drug delivery. However, coupling mucoadhesive properties to tablets has additional benefits. For instance, it offers efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio and facilitates a much more intimate contact with the mucus layer. The ability to target any mucosal tissue, including those in the gut, with mucoadhesive tablets allows for both localised and systemic controlled drug release. Mucoadhesive tablets are attached to the mucosal cells of the gastric epithelium to administer medicines with localised action. Due to their prolonged drug release, decreased frequency of drug administration, and increased patient compliance, mucoadhesive tablets are extensively used. Mucoadhesive tablets' main flaw is that they aren't physically flexible, which results in poor patient compliance for prolonged and repetitive use.[28-30]

Films:

Because they are more flexible and comfortable, mucoadhesive films may be chosen to adhesive tablets. Additionally, they can get around the mucosa's comparatively brief time of residence for oral gels, which is readily washed away and eliminated by saliva. Additionally, the films assist in protecting the wound area in the local delivery of oral diseases, which helps to lessen pain and improve the effectiveness of treatment. The perfect film should be soft, pliable, elastic, and strong enough to resist breaking under the strain of mouth movements. To stay in the mouth for the desired amount of time and have the desired effect, it must also have excellent mucoadhesive strength. If there is swelling of the film, it should not be too severe to cause pain.[31]

Patches:

Patches are laminates made up of a mucoadhesive surface for mucosal attachment, an impermeable backing layer, and a reservoir layer that contains the medication and releases it gradually. The methods used for transdermal drug delivery are comparable to patch systems.

Solvent casting and straight milling are two techniques used to make adhesive patches. The intermediate sheet from which patches are punched is produced by pouring a drug and polymer solution onto a backing layer sheet and then allowing the solvent(s) to evaporate. The direct milling method involves formulation ingredients are uniformly combined and compressed to the desired thickness before being cut or punched into patches of a specific size and shape. To regulate the direction of drug release, stop drug loss, and lessen the device's deformation and disintegration during the application time, an impermeable backing layer may also be used. [32-33]

Gels and Ointments[34-35-36-37-38-39-40-41] :

Gels and ointments are examples of semisolid dosage forms that have the benefit of being simple to spread throughout the oral epithelium. As opposed to tablets, patches, or films, semisolid dosage forms may not provide the most precise medication dosage. The use of mucoadhesive formulations has improved the gels' poor retention at the application location. Hyaluronic acid, carbopol, sodium carboxymethylcellulose, and xanthan gum are a few mucoadhesive polymers that experience a phase shift from liquid to semisolid. They are made of polymers that physically entrap drug molecules for later slow release via diffusion or erosion. These polymers are hydrated in an aqueous environment to create these compounds.[39] An prolonged retention period in the oral cavity, sufficient drug penetration, high efficacy, and patient acceptability are all provided by the use of mucoadhesive gels. The local distribution of pharmaceuticals for the treatment of periodontitis, an inflammatory and infectious condition that results in pockets forming between the gum and the tooth and can ultimately result in tooth loss, is a significant application of adhesive gels. When included in formulas with antimicrobials that are simple to inject with a syringe into the periodontal pocket, mucoadhesive polymers may be helpful for treating periodontitis.[39-41] HPMC has been used as a component in adhesive ointments. Additionally, an extremely viscous gel that could stay on the tissue for up to 8 hours was created from carbopol and hydroxy-propyl-cellulose for ointment dosage forms.[2]

Table No.3: Reported Buccoadhesive Drug Delivery System

Sr. No.	Category	Example	Dosage type	Polymer
1	NSAIDS	Diclofenac sodium [27], Piroxicam [28] Flurbiprofen [29]	Tablet	Cashnew nut tree gum, HPMCK4M, Carbopol, Chitosan, Sodium CMC.
2	Anti-Hypertension	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.
3	Anti-emetic	Domperidom [36], Granisetron hydrochloride [37]	Tablet	Carbopol934P, Metocel K4M, Chitoan, Sodium alginate, HPMC 50cps.
4	Anti-diabetic	Rapaglinide [38]	Tablet	Carbopol 934P, HPMC, Sodium CMC, HEC.
5	Bronchodilator	Salbutamol sulphate [39]	Tablet	Carbopol 934P, HPMC, Sodium CMC, HEC.
6	Vasoconstrictor	Sumatriptan [40]	Tablet	Chitosan, HPMC K4M, Sodium alginate.
7	Anti-viral	Acyclovir [41]	Tablet	Carbopol 943P, HPMC K100M.

Evaluation of Buccal Drug Delivery Systems:

Drug-Excipients Interaction Studies:

X Ray Diffraction is a technique that can be used to identify the crystalline properties of both the drug and the excipient, and it can also detect any drug-excipient interactions that may cause changes in the crystalline structure. Fourier Transform Infra-Red Spectroscopy can be used to identify the functional groups present in the drug and excipient molecules and can be used to detect chemical changes that may occur during the formulation process. Thin layer chromatography is a valuable tool for separation and identification of constituents in complex mixtures, including drugs and excipients.

In summary, these analytical techniques are important tools in the development and manufacturing of solid dosage forms, allowing for the identification and characterization of drug-excipient interactions, thus aiding in the formulation of stable and effective drugs. [57]

Physical Evaluation:

It involves uniformity in the content, weight, and thickness. By comparing the average weight of ten arbitrarily chosen patches from each batch with each individual patch, weight variation evaluation was carried out. The film's thickness needs to be measured at five different points (the centre and four ends), after which the mean thickness should be determined. Air bubbles, samples with nicks or tears, and samples with a mean thickness variation of more than 5% are excluded from examination. Each formulation's three 20 mm-diameter patches were placed separately in 100 ml volumetric flasks with 100 ml of pH 6.8 phosphate buffer solution, which was then constantly stirred for 24 hours. The liquids were filtered, appropriately diluted, and subjected to UV spectrophotometer analysis. The ultimate reading was calculated using the average of three patches.[20]

Surface pH:

In order to check for potential adverse effects in vivo, the pH of the buccal patch's surface was measured. It is important to maintain the surface pH as near to neutral as possible because an acidic or basic pH may irritate the buccal mucosa.[59] For this, a composite glass electrode was employed. The pH of the buccal patches was determined by putting an electrode against the patch's surface for one minute and allowing it to equilibrate.[60] The

buccal patches were kept in contact with 1 ml of distilled water (pH 6.5 0.05) and allowed to swell for two hours at room temperature.

Swelling Index of the Natural Mucoadhesive Agent:[61]

The mucoadhesive polymer is weighed, put through #80 sieves, put in a petri plate with 10 ml of distilled water, shaken every ten minutes, and left for three hours at room temperature. The water is removed after 1 hour and the weight of the mucoadhesive polymer is noted after 3 hours. Three occasions' averages are computed.

$$\text{Index of swelling} = [(W2-W1)/W1]$$

Were, W1 = the weight of the natural mucoadhesive agent prior to swelling, and W2 = the weight of the natural mucoadhesive agent following expansion.

Palatability Test:

A palatability test is carried out based on the flavour after the bitterness and the physical appearance of the substance. According to the criteria, each batch is given an A, B, or C rating. The formulation is regarded as average if it receives at least one A mark. When a composition receives two A grades, it is deemed to be good, and when it receives three A grades, it is deemed to be very good. [62]

Grades:

A = very good,

B = good,

C = poor

Ex Vivo Mucoadhesive Strength:

Using a modified balance technique, ex vivo mucoadhesive strength is evaluated. Within two hours of slaughter, acquire and use fresh buccal mucosa from rabbits or sheep. The underlying fat and loose tissues were divided, allowing the mucosal membrane to separate. The mucosal membranes were cleaned with distilled water before being heated to 370°C for phosphate solution (pH 6.8). Cut into minute pieces, the buccal mucosa was once more washed with phosphate buffer. (pH 6.8). The glass vial containing the phosphate buffer was attached to a portion of buccal mucosa. Before the research, the two sides of the modified

balance were made equal by adding a 5 g weight to the pan's right side. The right side of the pan had a weight of 5 g removed, which caused it to descend and place the tablet over the mucosa. Five minutes of contact time were spent maintaining the balance in this posture. Using an infusion set of 100 droplets per minute, water equivalent to weight was slowly added to the right side of the pan until the tablet separated from the mucosal surface. This detachment force provided information on the buccal tablet's mucoadhesive power in grammes. The phosphate buffer (pH 6.8)-filled glass beaker was securely sealed, allowing the glass vial to only touch the mucosal surface at a temperature of 37 °C ± 1 °C. Cyanoacrylate glue was used to attach the buccal tablet to the bottom of a rubber stopper.[63]

Ex- Vivo Mucoadhesive Time:

the period of time that passed after the ex vivo mucoadhesion test was conducted on sheep or rabbit buccal tissue that had just been surgically removed. Fresh buccal mucosa was affixed to a glass slide, and the mucoadhesive core side of each tablet was moistened with a drop of phosphate buffer (pH 6.8) and applied. lightly with a finger tip for 30 seconds to the sheep buccal mucosa. The glass plate was then placed in a beaker that contained 200 ml of phosphate buffer with a pH of 6.8 and was maintained at 37 °C plus or minus 1 °C. Tablet adhesion was tracked for 12 hours while a 50 rpm stirring rate was used to mimic the buccal cavity environment after two minutes. The mucoadhesion time was defined as the amount of time it took for the tablet to separate from the buccal epithelium.[64]

In Vitro Drug Release:

The rotating paddle technique described in United States Pharmacopoeia (USP) XXIII was used to examine the rate of drug release from bilayered and multilayered tablets. The phosphate buffer with a pH of 6.8 serves as the breakdown medium. The experiment was conducted at a temperature of 37 0.5 C and a rotational speed of 50 rpm. Instant adhesive was used to adhere the buccal tablet's backing layer membrane to the glass disc. (cyanoacrylate adhesive). The disintegration vessel's bottom was given over to the disc. Five millilitres of the sample were removed and replaced with new medium at preset intervals of time. After being properly diluted, the materials were filtered through Whatman filter paper and subjected to UV spectrophotometry analysis.[65]

In Vitro Drug Permeation:

The in vitro buccal drug permeation research of Drugs through the buccal mucosa of sheep or rabbit is carried out at 37°C using Keshary-Chien or Franz type glass diffusion cells. It contains the donor and receptor sections, both of which were tied with brand-new buccal mucosa. The buccal tablet's core side was facing the mucosa, and the sections were firmly fastened. One millilitre of phosphate buffer (pH 6.8) is put in the donor section, and seven millilitres are put in the receptor compartment. By agitating the receptor compartment at 50 rpm with a magnetic bead, the hydrodynamics state was kept. Using a UV spectrophotometer, a one-ml sample can be taken at preset intervals and tested for drug content at a suitable nm.[66]

Stability study in human saliva according to ICH guidelines:

For each batch, a stability analysis of quickly dissolving films is conducted. The films were assessed for physical appearance, drug content, and disintegration time after a preset amount of time. Up to three months, the stability research of the improved mucoadhesive patch formulation was conducted at 40°C, 37°C, and 75°RH. The values of all parameters remained unchanged after three months, with the exception of the values of volume entrapment efficiency, percent elongation, and percent drug release after eight hours, which underwent sizable alterations.[67]

Measurement of mechanical properties:

Using a motorised test stand (Ultra Test, Mecmesin, West Sussex, UK) with a 25kg load cell, a microprocessor-based advanced force gauze was used to evaluate the mechanical properties of the patches. A film strip measuring 60 x 10 mm and free of visual flaws was cut, then it was placed between two clamps that were spaced 3 centimetres apart. The strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke, whereas the lower clamp was kept stationary. Clamps were intended to secure the patch without crushing it during the evaluation. At the moment the strip split, the force and lengthening of the film were captured. Using the formula, the tensile strength and elongation at break values were determined.[68]

Tensile Strength (kg. mm$^{-2)}$

$$\frac{\text{Force at break (kg)}}{\text{Initial Cross Sectional Area of The Sample (mm}^2\text{)}}$$

Elongation at break (%. mm^{-2}) =

$$\frac{\text{Increase in Length (mm)}}{\text{Original Length Cross Sectional Area (mm}^2\text{)}} \times 100$$

Folding Endurance:

One patch was folded at the same location repeatedly until it broke, or it was folded manually up to 300 times, which was deemed sufficient to show good patch properties. The measure of folding endurance is determined by how many times the patch could be folded in the same location without breaking. Five patches are used for this evaluation.[69]

Viscosity:

aqueous solutions made with the same quantity of plasticizer and polymer as the patches. The viscometer is a Brookfield model LVDV-II connected to helipath spindle number four. At ambient temperature and 20 rpm, the viscosity was determined. The values that were reported represent the mean of three analyses.[70]

Ageing Bioadhesive:

For six months, patches were housed in petri dishes coated with aluminium foil and kept in an incubator set at 37.5 °C and 75 % RH. The stored patches were tested after 1, 2, 3, 4, 5, and 6 months for changes in release behaviour, residence duration, appearance, and drug content. The statistics showed the average of three conclusions. After six months of storage, scanning electron microscopy was used to compare the fresh and old pieces of medication.[71]

CONCLUSION:

This review of mucoadhesive buccal drug delivery systems is likely to be a helpful piece for the competent design of newer or novel mucoadhesive dosage forms. Mucoadhesive dosage form has numerous uses, including the development of novel mucoadhesives, device layout, permeation enhancement, and mucoadhesion mechanisms. With the advent of a large number

of new drug molecules as a result of medication discovery, mucoadhesive drug delivery will play an increasingly important role in delivering these molecules.

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