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Buccal Drug Delivery System: A Comprehensive Review

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ABSTRACT

The buccal area of the oral cavity is an ideal target for administering the desired medicine, as it helps overcome the limitations of conventional drug administration. The occurrence of presystemic metabolism and drug depletion in the digestive tract can be avoided by administering the medicine orally. The buccal drug delivery system is an innovative technique of delivering drugs that offers several advantages, particularly in terms of oral administration. The duration of placing the medicinal formulations at the desired site could be prolonged. The structures directly come into contact with both the absorbing surface and the mucus membrane, thereby enhancing the therapeutic effects of the delivered medicine. In addition to its numerous benefits, the buccal drug delivery system has a few drawbacks. These include the fact that the buccal supply is limited to specific places and there is a significant risk of medicine loss due to the movement of saliva and swallowing. Furthermore, in the future, the sector of oral drug distribution will require secure and convenient substances that enhance the absorption of drugs across the buccal membrane.

KEYWORDS: Novel drug delivery, Buccal drug delivery, Improved efficacy, Oral delivery, Targeted location.

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1. INTRODUCTION:

The oral route is the most suitable method for administering medication to patients and the safest means to transfer it to the circulatory system. The lack of monitoring and identification of the gastrointestinal tract (GIT) process has been hindered by the oral administration of nearly all medications in conventional dosage forms.[1] The Buccal medication Delivery System (BDDS) is a modern way to medication delivery that aims to replace traditional drug administration routes.[2] The occurrence of drug side-effects can be significantly minimised, and the targeted distribution of drugs can be effectively performed using BDD (Bio-Distribution and Drug distribution).[3,4] The administration of medications through the buccal mucosa (BM) has garnered significant attention due to its simple accessibility.[5]

As time goes on, researchers working in the drug development sector concentrate on finding other ways to administer pharmaceutical products that may have prospective benefits and on fixing issues related to the oral route of administration. Despite being the most popular method for administering large medications, the oral route has some disadvantages, including local gastrointestinal distress, enzymatic breakdown inside the GI tracts, and first pass metabolism in the liver. [6].

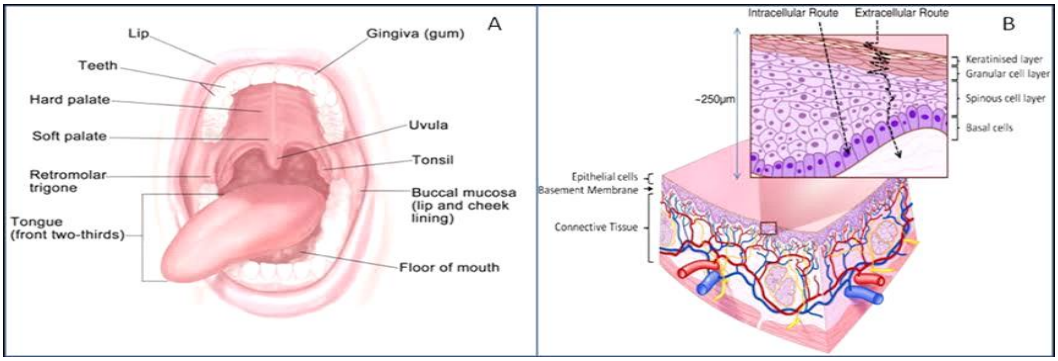

Fig. 1: (A) Anatomy of oral mucosa; (B) Transverse section of oral mucosa [6]

Significant advancements have been achieved in Bucco-adhesive drug administration to address specific challenges, such as first pass metabolism and low bioavailability, associated with regularly utilised dosage forms. Ascanio Sobrero conducted pioneering work on ballistic missiles (BM) in 1847 for the purpose of drug delivery. Since then, extensive research and development have been carried out in this subject.[7] In the BM region, there are several

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different types of cells, including the stratum basale, lamina propria, and stratum filamentosum.[8] BM is an optimal site for drug absorption, extended retention period, and excellent drug release in the context of controlled drug release (CDR). [9-12] The inner cheek region is bordered by the basement membrane (BM) region. Buccal formulations are placed in the midst of the gums and buccal pouch for both local and systemic therapy [13].

The aforementioned characteristics make the BM cavity an optimal pathway for the diffusion of small substances. The absorption of molecules is dependent on their interaction with the cell membrane and the manner in which they are administered. [14,15] The combination of active pharmaceutical ingredients (API) and hydrophilic polymer is utilised for buccoadhesion, which refers to the ability of a medicine to adhere to the buccal mucosa in order to enhance its bioavailability.[16] The BDDS offers numerous advantages, including a simple and efficient method for administration and ensuring patient compliance. Enzyme activity is limited due to the relatively immobile nature of the mucosa and smooth muscle. Therefore, medication administration is suitable in this context CDR [17-20]

Buccal mucosal drug delivery system (BDDS) allows for the administration of both local and systemic drugs. Ideally, substances with a partition coefficient ranging from 40 to 2000 and a pKa value between 2 and 10 are absorbed effectively.[21]

1.1 Anatomy of Oral Mucosa

Oral cavity membrane	Structure	Surface area (cm^2)	Thickness (µm)	Blood Flow (ml.min-1 .cm-2)
Buccal mucosa	non-keratinised	50.2	500-800	2.40
Gingival mucosa	Keratinised	…	200	1.47
Palatal	Keratinised	20.1	250	0.89
Sublingual mucosa	non-keratinised	26.5	100-200	0.97

Surface Area & thickness of Oral Cavity Membranes

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1.1.1 Drugs can be administered through the oral mucosa in three unique forms:
1. Sublingual administration of drugs involves delivering them across the layer of the tongue's front surface and the floor of the mouth.
2. Buccal supply: largely consists of the mucous membrane lining the cheeks and the buccal mucosa.
3. Local drug delivery: involved administering medications in all locations except for the two zones mentioned above.
These sites differ in terms of drug penetration, delivery rate, and their ability to sustain a delivery mechanism for a set time period in order to release medications into the mucosal membrane.[22]

1.2 Advantages and disadvantages of Buccal drug delivery system:
1.2.1 Advantages:

- Unlike other mucosal tissues, the buccal mucosa is comparatively porous and has a well-developed blood supply.
- Avoid the initial hepatic metabolism
- Demonstrates targeted treatment
- Certain drugs exhibit enhanced efficacy due to their prolonged interaction with the mucosa.
- Patient compliance is greater in comparison to alternative non-oral ways of drug administration.
- The formulation remains at the delivery site for an extended period due to adhesion and personal touch, enhancing the bioavailability of the active pharmaceutical ingredient (API) while requiring lower quantities of the API for disease treatment.
- Buccal drug delivery eliminates the adverse environmental factors associated with oral drug delivery.
- It is a mode of medication absorption that occurs without requiring any activation.
- Compared to rectal or transdermal routes, the presence of saliva ensures a significant amount of water for drug dissolution.

1.2.2 Disadvantages:

- The combined surface area of the oral cavity membranes available for medication absorption is 170 cm^2. Among these, nonkeratinized tissues, specifically the buccal membrane, make up 50 cm^2.

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- The barrier qualities of the mucosa.
- The drug becomes less concentrated due to the constant flow of saliva (0.5-2 litres each day).
- The risk of choking if the delivery system is swallowed involuntarily is a concern
- Ingesting saliva might lead to the elimination of dissolved or suspended medications. The unintentional elimination of the dose form. [23-27]

1.3 Mechanism of Buccal Absorption:

For bioadhesion to occur, three stages are involved:

- A close relationship involving a bioadhesive and a membrane, either as a result of the bioadhesive swelling or from a thorough soaking of the bioadhesive and membrane.
- The bioadhesive begins to pierce through the tissue.
- There is interpenetration of mucous between the bioadhesive chains. After that, low chemical bonds may stabilize.

The mechanisms of bioadhesion are explained by the following theories.
1. Wetting theory.
2. Theory of diffusion.
3. Theory of Adsorption.
4. Theory of fractures.
5. The theory of absorption
6. Theory of electronics [28,29]

1.4 Structure and Design of Buccal Dosage Form:
There are two types of buccal dosage forms:

1. **Matrix type:** which is a matrix-designed buccal patch medicament, adhesive, and additives are combined in the configuration.

2. **Type of reservoir:** A hollow in the reservoir-designed Buccal patch holds the medication and other ingredients apart from the adhesive. To regulate the direction of drug distribution, minimize patch deformation and disintegration while in the mouth, and stop drug loss, an impermeable backing is provided. Buccal absorption: Through the buccal mucosa, buccal absorption drives local or systemic effects. [30]

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1.5 Basic components of Buccal drug delivery system:

The basic components of Buccal drug delivery system are

1. Drug substance
2. Bio-adhesive polymers
3. Backing membrane
4. Permeation enhancers

Drug substance: It is necessary to determine if the targeted action is for a local or systemic effect, as well as for quick or sustained release, before developing mucoadhesive drug delivery systems. Pharmacokinetic characteristics should be taken into consideration when choosing a drug for the design of succinyl adhesive drug delivery systems. The medication ought to possess the qualities listed below. The medication should be taken in a modest typical single dose. Pharmaceuticals with a biological half-life of two to eight hours make excellent candidates for regulated drug delivery. When taken orally, the drug's Tmax exhibits larger fluctuations or higher values. Drugs taken orally may show signs of presystemic drug clearance or first pass impact. When a medicine is taken orally, absorption should be passive. [31,32]

1.6 ROUTE METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL [33,34,35**] :**

i) PERMATION ENHANCER: The epithelium lining the buccal mucosa is one of the main barriers in the BDDS. Delivering high molecular weight substances with poor buccal absorption rates is common, such as peptides and proteins. Absorption enhancers are substances added to drugs to help them pass through barriers and allow for buccal penetration. The majority of absorption enhancers were created with the goals of enhancing drug absorption, boosting efficacy, and reducing toxicity. The most widely used substances to improve absorption include bile salts, sodium dodecyl sulfate, and fatty acids.

ii) PRODRUGS: The bitter medications nalbuphine and naloxone, which are given to dogs through the buccal mucosa, generate excessive salivation and have a low bioavailability when swallowed. Naloxone and nalbuphine are used as prodrugs to overcome this; they have a relatively high bioavailability and cause no side effects**.**

1.7 BIOADHESION: [36,37,38,39]

Longer and Robison described the term bio-adhesion (also known as muco-adhesion). Bioadhesion is defined as a substance that can adhere to the biological tissues**.**

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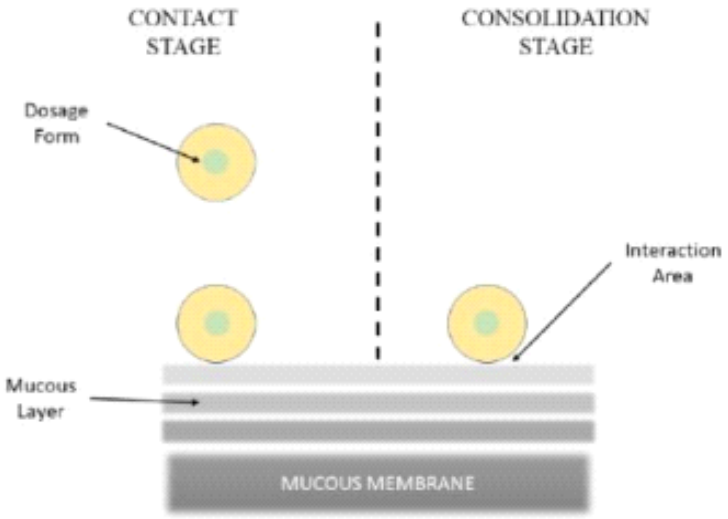
1.7.1 MECHANISM OF ADHESION:

There are two phases involved in the mechanism of bioadhesion.

1. The contact stage
2. The consolidation stage



Step 1: The contact stage is the first point of interaction between the drug's two surface polymers and the mucus surface. Following the polymer's soaking and swelling, these two surfaces physically combine.

Step #2 The stage of consolidation involves the bioadhesive polymer's interpenetration into the mucous membrane. The primary mechanism of attachment is the entanglement of the adhesive chemicals with the extended mucus chain, followed by the non-covalent interaction-induced creation of secondary bonds.

1.7.2 Theories of Bioadhesion:

It is simple to expand the theoretical framework for polymer-polymer adhesion to explain the bioadhesion of polymeric substances having living surfaces. The electronic, adsorption, wetting, diffusion, and fracture theories are among the pertinent theories.[40,41]

a) Electronic Theory:

According to electrical theory, there is probably going to be electron transfer when the bioabrasive polymer and the Different electronic topologies of glycoproteinic networks will result in the creation of two electrical charge layers at the bioadhesive interface.

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b) Adsorption Theory:

The adsorption theory states that bioadhesive systems stick to tissue.due to hydrogen bonding, Vander barriers, and associated forces.

c) Wetting Theory:

The formation of a strong adhesive bond requires intimate molecular interaction, which calls for investigation of the wetting equilibrium and dynamic interactions between the mucus and the bioadhesive candidate material. One crucial feature of liquid bioadhesive materials is
I. A contact angle that is zero or almost zero.
II. A comparatively low viscosity and
III. Close contact that prevents the entrapment of air.

The total of the two surface tensions and less than the interfacial tension determines the specific work of adhesion between the tissue and the bioadhesive controlled release system. [42]

d) Diffusion Theory:

A sufficiently deep layer of chains may emerge as a result of mucus and polymer chains interacting. The close contact of two polymers or two fragments of the same polymer is the diffusion mechanism. The polymer molecules and the dangling chains of the glycoproteinic network come into close contact during chain interpenetration. The concentration gradient causes the bioadhesive polymer chains to penetrate at speeds that rely on the chemical potential gradient and a macromolecule's diffusion coefficient via a cross-linked network.

Furthermore, for bioadhesion to occur, the bioadhesive medium must be well soluble in the mucus. Therefore, there should be as little variation as feasible between the solubility properties of the glycoprotein and the bioadhesive medium. As a result, the bioadhesive medium and glycoproteins need to have comparable chemical structures.

e) Fracture Theory:

The difficulty of separating two surfaces following adhesion to the adhesive bond is related to the facture theory of bioadhesion power. [43]

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2. NOVEL BUCCAL DOSAGE FORMS:

A few of the innovative buccal dosage formulations are tablets, films, patches, and powders; these are covered in brief below.A few of the innovative buccal dosage formulations are tablets, films, patches, and powders; these are covered in brief below.

2.1 Buccal mucoadhesive tablets :

These formulations are essentially dry and must be moistened before coming into contact with the buccal mucosa. Take a two-layered tablet, for example, with an inside cocoa butter center containing sodium glycocholate and insulin, and an adhesive matrix layer made of hydroxypropyl ellulose.

2.2 Patches and films :

The buccal patches consist of two laminations and an aqueous adhesive polymeric solution embedded atop a non-permeable backing sheath structure that splits into the required oval shape. Zilactin is a distinct muco-adhesive film composed of hydroxypropyl cellulose, alcohol, and organic acids. When applied to the buccal mucosa region, the film can stay that way for up to 12 hours.

2.3 Semi-solid formulations :

The patient compliance rate for gels and ointments that come in bio-adhesive forms is lower than that of solid muco bio-adhesive dosage forms, and the majority of dosage forms are used to deliver drugs locally. Orabase is an oral formulation that is gel-based and can be used for 15 to 150 minutes.

2.4 Powders :

as applied topically to the rat's belly, beclomethasone in powder form and HPC demonstrate a significant reduction in residency time as compared to oral solution, and 2.5 percent beclomethasone remains on the BM for over four hours.[44]

3. Factors affecting buccal absorption: [45]

Because there are numerous independent and interdependent variables that lower the absorbable concentration at the site of absorption, the oral cavity presents a complex environment for drug delivery

i. Membrane Factors: This includes the lamina propria, the degree of keratinization, the surface area that can be absorbed, the mucus layer of the salivary pellicle, the intercellular lipids of the epithelium, and the basement membrane. Furthermore, the thickness of the absorbent membrane, blood supply and lymph outflow, cell renewal, and enzyme content will all help to lower the rate and volume of medicine that enters the systemic circulation.

ii. Environmental Factors:

a) Saliva: The term salivary pellicle or film refers to the thin layer of saliva that covers the whole buccal mucosa lining. Salivary film has a thickness of 0.07 to 0.10 mm. The rate of buccal absorption is influenced by the film's thickness, content, and mobility.

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b) Salivary glands: The buccal mucosa's deep or epithelial part contains the small salivary glands. On the surface of the buccal mucosa, they continuously release mucus. Although mucus aids in the retention of mucoadhesive dose forms, it may act as a barrier to the absorption of drugs.

c) Movement of buccal tissues: The mouth cavity's buccal portion moves less actively. The use of mucoadhesive polymers is necessary to maintain the dosage form in the buccal region for extended periods of time, withstand tissue movements when speaking, and if feasible when swallowing or consuming food .

3. Composition of buccal patches: [45]

A. Active ingredient

B. Polymers (adhesive layer) : HEC, HPC, polyvinyl pyrrolidone(PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.

C. Diluents: Because of its high water solubility, flavoring qualities, and physico-mechanical attributes that make it appropriate for direct compression, lactose DC is chosen as diluents. Another example would be starch and microcrystalline starch.

D. Sweetening agents: Mannitol, sucrose, aspartame, etc.

E. Flavoring agents: Menthol, vanillin, clove oil, etc.

F. Backing layer : EC etc.38 Rao NGR, Shravani B, Reddy SM. Overview on Buccal Drug Delivery Systems. J Pharm Sci Res., 2013; 5(4): 80-88.

G. Penetration enhancer : Cyano acrylate, etc

H. Plasticizers : PEG-100, 400, propylene glycol, etc

4. Evaluations of Buccal Patch:

i. Surface pH: Buccal patches are placed on the surface of an agar plate and allowed to swell for two hours. Using a pH paper applied to the surface of the swollen patch the surface pH is determined. [24]

ii. Thickness measurements: An electronic digital micrometer is used to measure each film's thickness at five separate positions (the center and four corners). [46]

iii. Swelling study: Individual buccal patches (identified as W1) are weighed, then placed separately on 2% agar gel plates. They are then incubated at 37°C ± 1°C and checked for physical changes. Patches are taken off of the gel plates at regular intervals of one hour up to three hours, and any remaining surface water is carefully wiped away with the filter paper.

The swelling index (SI) is then computed using the following method after the swollen patches have been reweighed (W2). [47,48]

$$SI = \frac{(W2-W1) \times 100}{W2}$$

5. Water absorption capacity test: Agar plates prepared in simulated saliva (2.38 g Na^2HPO4, 0.19g KH^2PO4, and 8g NaCl per litter of distilled water adjusted with phosphoric

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acid to pH 6.7) are covered with circular patches with a surface area of 2.3 cm^2, which are then allowed to swell. The plates are then kept in an incubator that is kept at 37°C ± 0.5°C. Samples are weighed (wet weight) at intervals of 0.25, 0.5, 1, 2, 3, and 4 hours. They are then allowed to dry for 7 days at room temperature in a desiccator over anhydrous calcium chloride before the final constant weights are recorded. The following formula is used to determine water absorption (%): In this case, Wf is the final weight and Ww is the wet weight. Every film's enlargement is quantified. [49,50]

$$\text{Water uptake (\%)} = \frac{(W_w - W_f)}{W_f}$$

6. Ex-vivo bioadhesion test : Fresh sheep mouths were separated and given a pH 6.8 phosphate buffer wash. Gingival mucosa fragments are tied into a glass vial with an open mouth and phosphate buffer (pH 6.8) within. Tightly fitting this glass vial into a glass beaker with phosphate buffer (pH 6.8, 37°C ± 1°C) allows it to come into contact with the mucosal surface only. A rubber stopper's lower side is adhered to the patch using cyanoacrylate adhesive. A 5-g weight is used to balance two balance pans. The pan on the left side, which was loaded with the patch over the mucosa, had the 5-g weight removed. The equilibrium is maintained in this position for a duration of five minutes.Water is introduced to the right-side pan gradually at a rate of 100 drops per minute until the patch separates from the mucosal surface. The measurement of mucoadhesive strength was given by the weight, expressed in grams, needed to separate the patch from the mucosal surface. fig.1 [51,52,53]

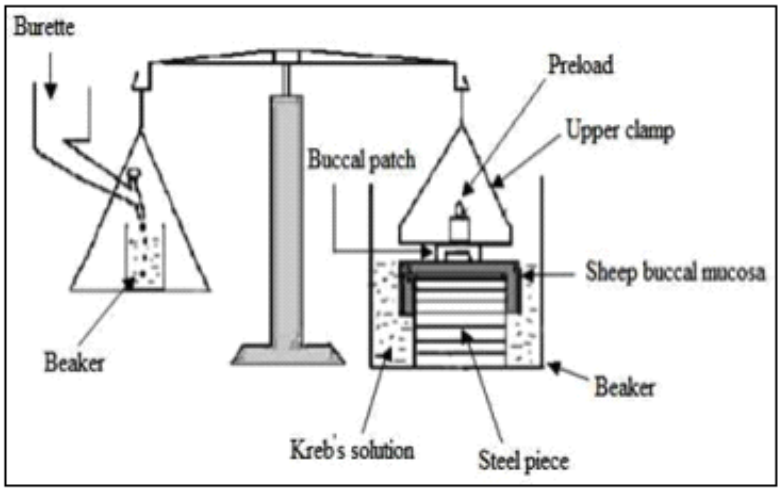

FIGURE 2: MEASUREMENT OF MUCOADHESIVE STRENGTH

7. In vitro Drug Release: The drug release from the bilayered and multilayered patches is investigated using the rotating paddle method described in United States Pharmacopeia (USP) XXIII-B. Phosphate buffer with a pH of 6.8 served as the dissolving media. The release is carried out at 37°C ± 0.5°C and 50 rpm of rotation. Using instant adhesive, the

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buccal patch's backing layer is affixed to the glass disk. The disk is assigned to the dissolution vessel's bottom. At predefined intervals, five milliliter samples are taken out and replaced with new media. After the proper dilution, the samples were filtered using Whatman filter paper and examined for drug content**.**Sheep and rabbit buccal mucosa are used for the in vitro buccal permeation, which is carried out at 37°C±0.2°C using a glass diffusion cell of the Keshary-Chien/Franz type. In the space between the donor and receptor compartments, new buccal mucosa is mounted.The buccal patch is positioned with the compartments clamped together and the core facing the mucosa.The donor compartment has buffer inside of it. [54.55,56]

8. Ex-vivo Mucoadhesion Time: The ex-vivo mucoadhesion time measured on newly cut buccal mucosa (sheep and rabbit) following the application of the buccal patch. The freshly cut buccal mucosa is connected to the glass slide, and a mucoadhesive patch is applied with a fingertip's mild pressure for 30 seconds after being moistened with one drop of phosphate buffer pH 6.8. After that, the glass slide is placed in a beaker that has 200 milliliters of pH 6.8 phosphate buffer in it and is maintained at 37°C ± 1°C. Following two minutes, the environment of the buccal cavity is simulated using a 50 rpm stirring rate, and patch adhesion is tracked for a whole day. It is noticed when the patch's color, form, collapse, and drug content change**.**

9. Measurement of mechanical properties: A tensile tester is used to assess the mechanical properties of the films (patches), such as elongation at break and tensile strength. A 60 x 10 mm film strip that is free of visible flaws is cut and placed between two clamps that are 3 centimeters apart. These clamps are made to hold the patch in place during the test without crushing it; the upper clamp moves at a speed of 2 mm/sec to draw the strips apart until the strip breaks, recording the force and elongation of the film at that moment. The formula 36 is used to calculate the tensile strength and elongation at break values. In this formula, M stands for mass in grams, g for acceleration due to gravity (980 cm/sec2), B for specimen width in centimeters, and T for specimen thickness in centimeters.The force at break (kg) per specimen's initial cross-sectional area (mm^2) is known as the tensile strength (kg/mm2) 7.[57]

10. Stability study in human saliva: The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate petridishes containing 5ml of human saliva and placed in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3 and 6 hours), the dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated.

Buccal adhesive solutions are very advantageous in terms of patient compliance, economy, low enzymatic activity, accessibility, administration, and removal. The systemically given

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medications' bioavailability is enhanced when buccal adhesive drug delivery devices adhere to mucosal membranes, increasing the drug concentration gradient at the absorption site. Additionally, in order to limit adverse effects that can result from systemic drug delivery and to target local diseases at the mucosal surface (such as mouth ulcers), buccal adhesive dosage forms have been used. Now a days, scientists are searching for other cutting-edge drug delivery systems outside of the conventional polymer networks**.**

At the moment, oral dosage forms such as liquids, gels, and solid dosage forms are economically successful. Future developments in buccal adhesive medication delivery will focus on delivering tiny proteins and peptides and developing vaccine formulations.

CONCLUSION: This review of the mucoadhesive buccal medication delivery method is likely going to be helpful in the skillful creation of a unique or updated mucoadhesive dosage form. Mucoadhesive dosage forms have uses from a number of angles, such as the development of new mucoadhesives, device design, improving penetration, and mucoadhesion mechanisms. As a result of drug discovery, a huge number of new drug compounds have been introduced, and mucoadhesive drug delivery will become increasingly important in delivering these molecules**.**

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