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Review Article

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AN INSIGHT: MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT

The adhesion between two materials, at least one of which is a mucosal surface, is commonly referred to as mucoadhesion. Mucosal drug delivery has been receiving a lot of attention in the last few decades. Mucoadhesive dosage forms offer a controlled rate of drug release for better therapeutic outcomes by allowing for extended retention at the site of application. When dosage forms are applied to mucosal surfaces, they may help medication molecules that are not well suited for oral administration, like those that experience prolonged first-pass metabolism or acid breakdown. A dosage form's capacity to adhere to mucosal tissue depends on several factors, such as the composition of the mucosal tissue and the physicochemical characteristics of the polymeric formulation. An overview of the numerous aspects of mucoadhesion, mucoadhesive materials, factors influencing mucoadhesion, methods of evaluation, and, lastly, buccal mucoadhesive drug delivery systems are the objectives of this review article.

KEYWORDS: Mucoadhesion, Buccal route, Mucosal surfaces, Polymer.

INTRODUCTION

Delivery of drug molecules via oral route is most desired in comparison to other administration routes but it also has some restrictions including primary hepatic metabolism, degradation of drug by enzymes within the alimentary canal, and toxicity in GI that limits oral administration of some drugs, mostly proteins and peptides.[1] Most pharmaceutical dosage forms are designed for immediate release which has some drawbacks such as frequent administration is required for the drugs that have a short half-life, poor patient compliance, and higher chances of adverse effects due to fluctuation in drug levels, particularly in case of drugs with small therapeutic index.

Several technological innovations were developed that brought the advancement of delivering drug in controlled way that may modernize drug therapy, offers a variety of therapeutic benefits, and overcome the shortcomings of traditional systems of drug delivery.[2] To enhance the efficacy of pharmaceutical treatments, there has been a growing emphasis on creating novel drug delivery systems in recent years. Among these, mucoadhesive drug delivery systems based on polymers or biopolymers that are meant for oral usage have attracted a lot of interest.[3]

Drug delivery via buccal mucosa is one the good substitute among the number of routes of administration as it has several merits over the other routes for systemic delivery of medicine such as directly deliver drug to systemic, avoidance of first-pass effect, and circumvention of pre-systemic elimination within the gastrointestinal (GI) tract. These features make it a more appealing and feasible location for medicine delivery directly into the blood.[4]

Buccal drug delivery systems offer a promising route for drug delivery not only to the buccal mucosa for the treatment of oral conditions but also for systemic delivery by absorption through the mucosa to the systemic circulation at a predetermined and controlled rate.[5,6] In addition, the buccal mucosa permits prolonged retention of a dosage form, especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route.[7] It is also possible to administrate drugs to patients who have difficulties in swallowing.[8]

Moreover, the buccal cavity is more convenient for self-medication and the dosage form can be promptly removed/interrupted from the buccal cavity in case of toxicity or adverse drug reaction. Various opportunities for mucoadhesive buccal drug delivery like films, gels, tablets, sprays and particulate dosage form are present for mucoadhesive drug delivery system to deliver the local or systemic release of the medicament in the buccal region.[9]

Contrary to the conventional buccal tablets, the mucoadhesive tablets are, however, static in its position

in the buccal cavity.[10] In other terms, the mucoadhesive buccal tablets are particularly promising they can adhere to the mucosal surface in the suitable regional spot in the mouth,[11] thus facilitating retention of the drug at the site of application, while providing a controlled rate of drug release (deliver the drug over a period of time) for better therapeutic outcome.[12] This area of research is driven by the need to improve drug delivery, especially for drugs with low bioavailability or those requiring sustained release.

Polymer mucoadhesive oral administration has increased in popularity over the past 20 years because of its unique physicochemical features. It is one of the most promising mucoadhesive oral delivery methods. One of the adhering surfaces must be a mucous membrane or tissue for mucoadhesion to occur. Mucoadhesion, in terms, is a subset of adhesion that is defined as the capacity of a material to adhere to any biological surface.[13] Specifically, the adhesive connection to a mucus membrane is known as mucoadhesion. It occurs on specific biological surfaces, such as epithelial tissue or the mucus coating on the surface of a tissue. The term mucoadhesion was coined by Leung and Robinson,[14] who defined it as the interaction between the surface of a mucin (a type of glycoprotein) and a synthetic or natural polymer.[15,16]

Ideal characteristics of buccal adhesive drug delivery system[17]

- It Should facilitate the rate of drug absorption
- It Should not cause any inconvenience or irritation to the patient
- It Should be stick to the site of attachment for a few hours.
- It Should be discharging the medication in a controlled manner and,
- It Should allow the release of medication in a unidirectional way toward the mucosa.

Advantages of buccal drug delivery system[18,19,20]

- It has a relatively larger surface area and a rich blood supply
- Drug is effortlessly administered and extinction of therapy in emergency may be facilitated.
- In unconscious and trauma patient's drug can be administered.
- Drug has high bioavailability because it bypasses first pass metabolism.
- Some drugs are unstable in acidic environment of stomach can be administered by buccal delivery.
- Drug absorption occurs by passive diffusion does not require any activation.
- Due to close contact with the absorbing membrane surface (Buccal mucosa is highly vascularized) thus, rate of absorption is high.
- Fast onset of action and extended drug release.

Limitation of mucoadhesive buccal drug administration[18,20,21]

- This route cannot administer drugs in large doses.
- Drugs not stable at buccal pH are challenging to deliver.
- Limits eating and drinking.
- Possibility of patient's swallowing the formulation.
- This route cannot administer drugs that have a bitter taste or an unpleasant odour or causes mucosal irritation.
- Surface area available for absorption is limited.
- Medicines absorbed by diffusion can only be administered.
- Continuous salivation (0.5-2 L/Day) causes the medication to dissolve.
- When saliva is swallowed, the dissolved or suspended drug is lost and eventually the dosage form is unwillingly removed.

Oral Anatomy and Physiology

Several publications, have extensively deliberated the structure and composition of the buccal mucosa.[22,23] The Buccal mucosa having of three distinct layers, epithelium, basement membrane, and connective tissues. oral cavity's basement membrane supported by a Connective tissue, which is lined by epithelial layer.[24]

- Two types of epithelium are found in the oral cavity

I. Non-keratinized epithelium covers the mucosal layer over the soft palate, tongue's ventral surface, mucosa of alveolar, the vestibule, the lips, and the cheeks, and
II. Keratinized epithelium covers the hard palate and inflexible regions. Originating from the basal cells, epithelial cells mature and modify their shape while expanding in size during the movement toward the surface.

According to the several literature survey, the oral mucosal epithelium in humans, dogs, and rabbits have thickness approximately 500– 800 mm.[25] The basement membrane is present between epithelium and connective tissues and have the function of necessary adhesion, as well as mechanical support to the epithelium. Lamina propria, also known as connective tissue, is made up of fibres of collagen, connective tissues layer, smooth muscles and blood vessels. The external carotid artery provides a rich arterial supply to the buccal mucosa. Among the major arteries, buccal artery supplying blood to the cheek lining located in the oral cavity, few facial artery branches, the posterior alveolar artery, and the infraorbital artery are also supplying the blood to the cheek lining.[26]

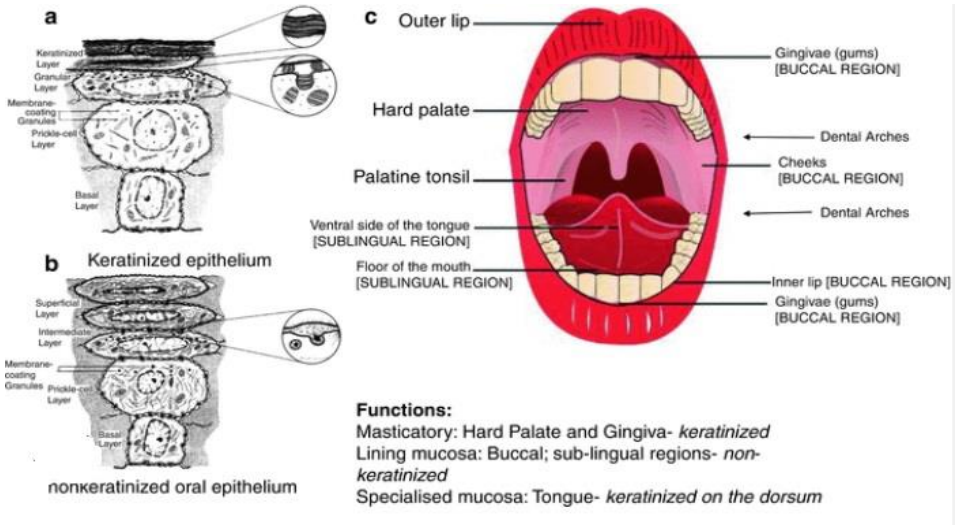

Figure: Representation of Anatomy and Physiology of the oral cavity.

Mechanism of mucoadhesion[27]

Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. It can be explained by 2 stages they are as follows:

1. **Contact stage:** It involves interaction between mucoadhesive material and mucous layer, upon contact with the mucous membrane, the formulation swells and spread over on it.
2. **Consolidation stage:** Mucoadhesive material present in the formulation is activated by the moisture which further plasticize the system and then allows the mucosal adhesive molecules to separate and connect through a weak Vander walls and hydrogen bonds.

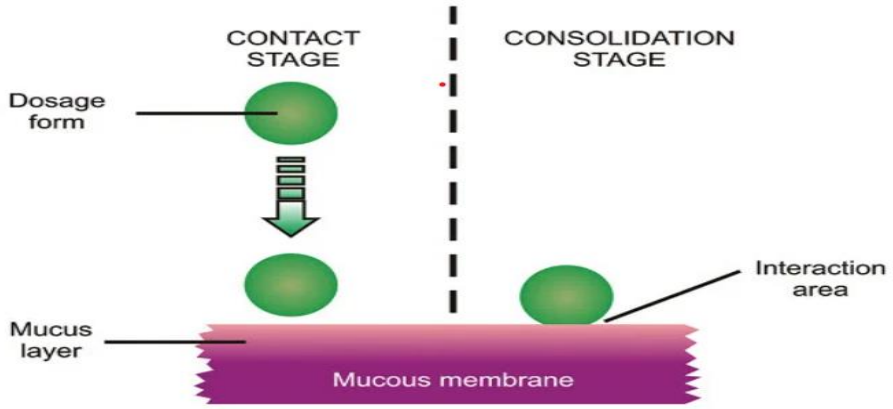

Figure: Mechanism of Muco-adhesion a) Contact stage b) Consolidation stage.[28]

Theories of mucoadhesion

Although the chemical and physical basis of muco-adhesion are not yet well understood, there are several theories adapted based on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.[29-37]

1) **Adsorption theory:** According to this theory, after an initial contact between two surfaces, the chemical bond will be formed between the atoms present over on a surface due to the surface forces acting between the chemical structure at the two surfaces, then the adhesion of the materials occurs.[30] When polar molecules or groups are present, they reorientate at the interface. Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding).[31,32]

Two types of chemical bonds resulting from these forces can be distinguished

- Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.
- Secondary chemical bonds having many different forces of attraction, including electrostatic forces, van der Waals forces, and hydrogen and hydrophobic bonds.

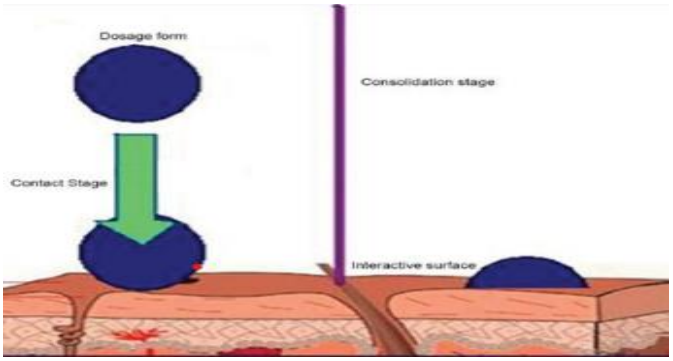

Figure: Process of consolidation in adhesion mechanism.

2) Wetting theory: this theory analyses adhesive and contact behaviour in terms of the ability of a liquid or paste to spread over on a biological system and it is predominantly applicable to liquid bio adhesive systems. Polymer with positive spreading coefficient will have good binding ability.[33]

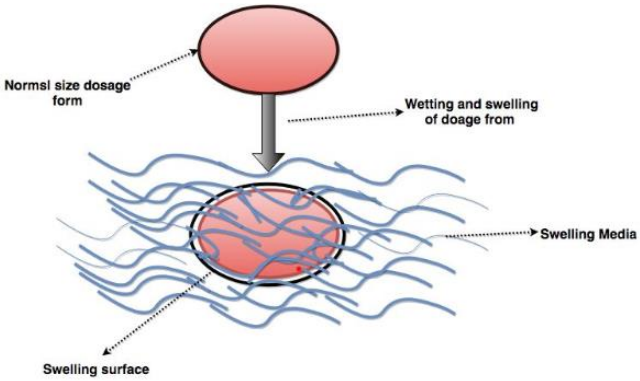

Figure: Shows penetration of dosage form into the surface or tissue of the mucosal layer by wetting or swelling mechanism.

3) Electronic theory: electronic theory explains about the electron transfer phenomenon between the adhesive polymer with a mucus glycoprotein network because of difference in their electronic structure. This outcomes in the formation of an electrical double layer at the interface. Adhesion mechanism occurs across the double layer due to attractive forces between them.[34]

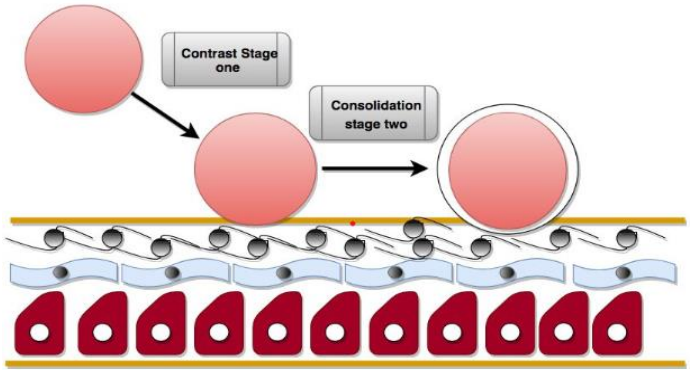

Figure: Indicates the stages concerned with mucoadhesion.

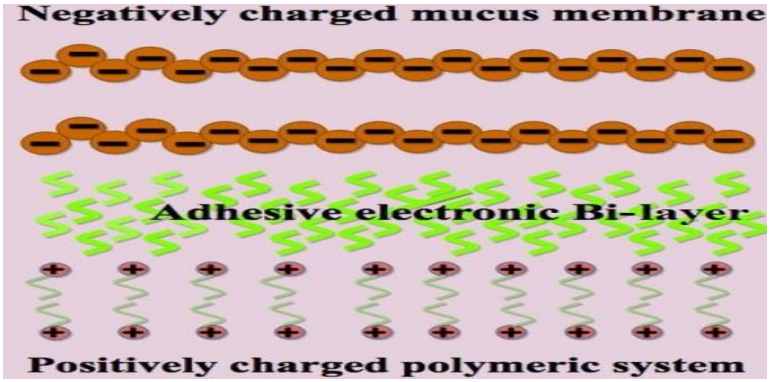

Figure: Adhesion between the mucus membrane (Negative charge) and the polymeric system (Positive charge), through differences in their electronic structure.

1) **Diffusion theory:** This theory is according to interaction between mucin layer strands and chains of polymer.[35] This theory describes that the mucus and polymer chains penetrate to a sufficient depth and are urged by a concentration gradient to form a semi-permanent adhesive bond. There are many reasons which are impact on the interdiffusion of polymer network like Mobility, diffusivity, contact time, flexibility and nature of mucoadhesive strands.[36]

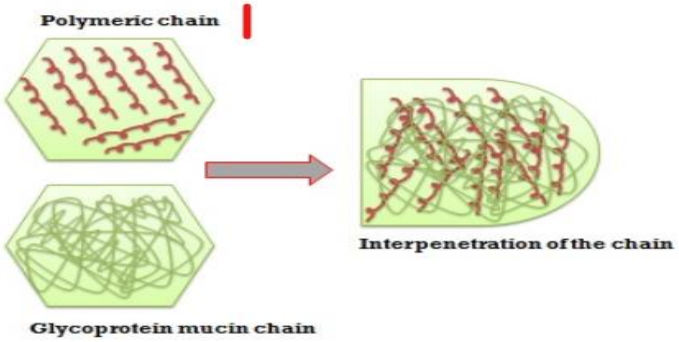

Figure: Diffusion Interlocking of the mucoadhesive polymer with glycoprotein mucin chain.

2) **Fracture theory:** This theory describes about the force required for the separation of two surfaces (detachment of polymer from the mucus after adhesion) after adhesion. Irregular surface of polymer and mucin gives better physical entanglement. [37]

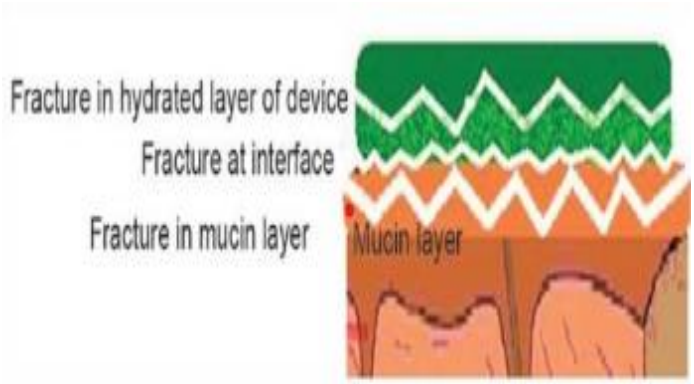

Figure: Fractures occurring for Mucoadhesion.

Factors affecting muco-adhesion

Mucoadhesion may be affected by a number of factors, including molecular weight, cross-linking, hydrophilicity, swelling, pH, and the concentration of the active polymer etc.

1) **Molecular weight:** Low-molecular-weight influences the interpenetration of polymer molecules, whereas higher molecular weights influence the entanglement. The maximum mucoadhesion influenced by an optimum molecular

weight with depends on the type of polymer and bioadhesive polymer.[38]

2) **Cross linking and swelling:** Cross-link density is inversely proportional to the degree of swelling. [39] The lower the cross-link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better the mucoadhesion. To achieve a high degree of swelling, a lightly cross-linked polymer is preferred. However, moisture presence is directly influencing the degree of swelling. The mucoadhesion of cross-linked polymers can be enhanced by the inclusion in the formulation of adhesion promoters, such as free polymer chains and polymers grafted onto the preformed network.[40]

3) **Hydrophilicity:** The bio adhesive polymers bear several hydrophilic functional groups, such as hydroxyl and carboxyl group. They allowed for hydrogen bonding with the substrate, swelling in aqueous media, thereby allowing maximal exposure of potential support sites. In addition, swollen polymers have the maximum distance between their chains leading to increased chain flexibility and efficient penetration of the substrate.[41]

4) **Charge and pH:** Some simplifications regarding the bioadhesive polymers charge have been made earlier, where non-ionic polymers have less amount of adhesion property compared to anionic polymers. According to Peppas and Buri, the strong anionic charge of the polymer is one of the imperative properties for muco-adhesion. Some cationic polymers like chitosan shows higher bioadhesive properties, primarily in a neutral or to some extent in alkaline medium. The membrane charge has no influence but the membrane pH can affect the mucoadhesion as it has impact on the ionized or un-ionized forms of the polymers.[42]

5) **Concentration of the polymer:** Ahuja stated that there is an optimum concentration of polymer corresponding to the best mucoadhesion. In highly concentrated systems, beyond the optimum concentration the adhesive strength drops significantly.[31]

6) **Other factors:** Other polymer and environmental related factors like spatial configuration of polymer, flexibility of the polymer chain, applied strength, initial contact time, disease status etc.,

Basic components of buccal drug delivery system

- Drug substance
- Bioadhesive polymers
- Backing membrane
- Permeation enhancers

Drug substance

The suitable drug substance can be selected on the basis of its pharmacokinetic properties (ADME properties). Before formulating the dosage forms, one has to been decided whether the intended action is for onset/prolonged release and for local/systemic effect.

Some characteristics of drug substances are as follows[43]

a) When the drug administered orally, drug absorption should be takes place a passive mechanism.
b) Half life of the drug candidate is 2-8 hours.
c) The conventional single dose should be small.
d) Tmax of the drug shows wider fluctuation or higher values when given orally.
e) Through oral route drug may exhibit first pass effect or presystemic drug elimination.

Polymers used in bioadhesive drug delivery system

Bioadhesive polymers can be water-soluble or -insoluble polymers that are swellable networks, which are joined by the cross-linking agents. These polymers have optimal polarity for adequate wetting while sufficient fluidity allowing the mutual adsorption as well as mutual penetration of the polymer and mucus.

Characteristics feature of ideal mucoadhesive polymer[44]

An ideal polymer has the following characteristics:

i. Polymer should be nondegradable, non-toxic, non-irritant and non-absorbable from the GI tract.
ii. Preferably form a strong non-covalent bond with the mucin layer of epithelial cell surfaces.
iii. It should adhere quickly to moist tissue and possess some site specificity.
iv. Drug can be easily incorporated and provide no hindrance to their release.
v. The polymer should not decompose on storage or during the shelf life of the dosage form.
vi. The cost of the polymer should not too high so that the prepared dosage form becomes inconvenient to be marketed.

Mucoadhesive/ Bioadhesive polymers

Table: Classification of mucoadhesive polymers.[45]

Classification properties	Types	Examples
Based on source	1. Synthetic polymer	Cellulose derivative, poly(acrylic acid) polymers, Poly(hydroxyethylmethylacrylate), Poly (ethylene oxide), Poly (vinyl alcohol), Poly (vinylpyrrolidone), Thiolated polymer
	2. Natural polymer	Tragacanth, Sodium alginate, Agarose, Guar gum,

		Xanthan gum, Karayagum, carrageenan, Chitosan, Soluble starch, Pectin, Gelatin.
Based on solubility	1. Water soluble polymer	Hydroxy Ethyl Cellulose, Hydroxy Propyl Cellulose, PAA, Sodium CMC, HPMC, Sodium alginate
	2. Water-insoluble polymer	Chitosan, Ethyl cellulose, Polycarbophil
Based on charge	1. Cationic	Chitosan, dimethyl amino ethyl-dextran, Amino dextran
	2. Anionic	Chitosan-EDTA, CMC, CP, pectin, PC, PAA, xanthan gum, sodium CMC, alginate
	3. Non-ionic	Hydroxy ethyl starch, PVA, PVA, PVP HPC, scleroglucan, poly (ethylene oxide)
Based on potential bioadhesive forces	1. Covalent	Cyanoacrylate
	2. Hydrogen bond	CP, PVA, PC, Acrylates
	3. Electrostatic bond	Chitosan
Based on Generation	1. First generation	Chitosan, dimethyl amino ethyl-dextran, Amino dextran Chitosan EDTA, CMC, CP, pectin, PC, PAA, sodium, xanthan gum, sodium CMC alginate, Hydroxy ethyl starch, PVA, PVP HPC, scleroglucan, poly (ethylene oxide)
	2. Second generation	Lectins, Thiolated polymers

Backing membrane[46]

Backing membrane plays a major role in attachment between the bioadhesive devices and a mucus membrane, the material should be inert and impermeable to the drug and penetration enhancer. Buccal bioadhesive patches with such a membrane improve patient compliance and stop medication loss. the most commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC etc.

Plasticizers[46]

The purpose of the plasticizers is to improve the drug delivery device's folding endurance. They give the dosage form minimal flexibility to increase patient compliance and acceptability. A few examples of plasticizers that are commonly utilized are propylene glycol, dibutyl phthalate, PEG-400, and PEG-600.

Permeation enhancers[47]

These are the chemicals or liquids used to improve the permeation of drug from device into the mucus membrane. The permeation enhancers work by following mechanisms. Mechanisms of action of permeation.

- By reducing the viscosity of mucus.
- By increasing the fluidity of lipid bilayer membrane.
- By countering the enzymatic barrier.
- By increasing the thermodynamic activity of drugs

Table Mucosal penetration enhancers.[48]

Classification	Examples
Surfactants	Anionic: Sodium lauryl sulphate, Sodium laurate. Cationic: Cetylpyridinium chloride. Nonionic: Poloxamer, Span, Tween Bile salts: sodium glycodeoxycholate, Sodium taurocholate.
Fatty acids	Oleic acid, Caprylic acid.
Cyclodextrins	a-, b-, g-cyclodextrins, methylated b- cyclodextrins.
Chelators	EDTA, Sodium citrate, Polyacrylates.
Positively charged polymers	Chitosan, Trimethyl chitosan
Cationic compound	Poly L-arginine, L- lysine

Buccal formulations

Some criteria considered during formulations of different types of buccal formulations[49]

1. The dimensions of the delivery system differ depending on the formulation type; for example, a flexible buccal patch can have an area of approximately 10-15 cm^2, while a buccal tablet has a diameter approximately 5-8 mm.
2. The most acceptable buccal patches are mucoadhesive ones with a surface area of 1-3 cm^2.
3. The shape of delivery system may also vary, although for buccal drug administration, an ellipsoidal shape is most accepted.
4. The thickness of the delivery device is usually restricted to only a few mm.
5. The location of delivery device is also important.

6. The maximum duration of buccal drug retention and absorption is approximately 4-6 hr. because food and/or liquid intake may require removal of delivery device.
7. The physiology of mucus membrane under disease condition needs to be considered.

Types of buccal formulation

- Buccal tablets
- Bioadhesive microspheres
- Bioadhesive wafers
- Bioadhesive lozenges
- Buccal patches and films.
- Buccal semisolids (Gels and Ointments)
- liquid dosage form.

2. Buccal tablets[50]

- Adhesive tablets are held between the gum and cheek.
- Tablets are generally flat and elliptical or capsule shaped.
- Lozenges and troches are other types of tablets used in oral cavity intended to exert a local effect in the mouth or throat.
- Buccoadhesive tablets may be monolithic or bilaminated.
- Monolithic is multidirectional release while bilayerd contain core layer and backing layer.
- Backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer.
- Backing layer avoids sticking of the tablet to the finger during application

Advantages

- A wide range of drugs, from soluble to soluble, low dose to high dose, and hydrophilic to lipophilic, can be developed for the buccal tablet.
- Buccal tablets are flat, smaller, and held at the locati on until release and/or dissolution are finished, in co ntrast to conventional tablets.

Disadvantages

- They are solid, which causes a slight amount of discomfort in the buccal cavity.

3. Bioadhesive films/ patches[51]

The bioadhesive patches or film are recommended over tablet because of their comfort and flexibility. They are designed to allow for contact between the mucosa and the bioadhesive formulation. A drawback that avoids the drug from being released under control for a longer duration of time depends on the patch's thickness. In case of drug containing reservoir layer type; drug is released in controlled manner. Patches and film are mostly preferred for local action to treat oral diseases. There are many methods used for formulation of patch or films such as solvent casting method, hot melt extrusion technique, direct milling, semisolid casting, solid dispersion extrusion etc. Among that solvent casting is most popular method and widely used.

4. Buccal Gels and Ointments[52]

As the benefits of ointment and dispersion gel have gained attention. Since they lack the accuracy of unit dosage forms like tablets, patches, or films, they are primarily used for local actions where dosage accuracy is either non-existent or not a concern.

Advantages: Local application of steroidal gel for treatment of mucosal ulceration in order to decrease the side effect of steroids.

Disadvantages: It has less patient acceptability than other mucoadhesive formulation.

5. Liquid dosage form

These are available in form of solution or suspension of drug in suitable vehicle. there are many liquid dosage forms that are available in market such as mouthwashes, mouth freshener, and are generally used for local delivery of drugs. Wide varieties of polymers are use from that chitosan has greatest binding capacity than other. Viscous liquid formulations are preferred to coat buccal cavity either as vehicle or as protectant.[53]

Evaluation of buccal mucoadhesive dosage forms[54,55,56]

Weight variation: Each of the twenty tablets will be weighed separately. The average weight of the tablets will then be calculated, followed by the weight variation.

Hardness: The hardness of the tablets will determine using a Monsanto hardness tester.

Friability test: The Roche friabilator will be used to test the tablets for friability. Six tablets are weighed and subjected to the coupled effects of shock and abrasion in the friabilator's plastic chamber, which rotates at 25 rpm for a period of four minutes. The tablets are then dust-treated and weighed again.

Content uniformity: In a glass pestle and mortar, ten tablets will be precisely weighed and ground into a powder. A precise weight equivalent to 5 mg of pure medication is taken, and the assay is carried out in triplicate using UV-Visible spectrophotometry at 228 nm.

Surface pH: For insight into the possibility of any oral cavity irritation, the tablets' surface pH will be measured. For two hours, the tablets will continue to stay in contact with the simulated saliva solution. The pH will be showed by placing the electrode against the formulation's surface.

Drug-excipients interaction studies: Studies on the interactions between drugs and excipients are crucial to the formulation and development of solid dosage forms. To evaluate potential drug-excipient interactions by

means of research thin layer chromatography, Fourier transform infrared spectrum (FTIR), X-ray diffraction (XRD), and differential scanning calorimeter (DSC) can all be employed. The differential scanning calorimeter is used to quickly assess potential incompatibilities because it can display changes in appearance, melting endotherm and exotherm shifts, and variations in the reaction's corresponding enthalpies.[57]

Swelling studies

Swelling increases the weight of patch

A 1x1 cm2 drug-loaded patch was preserved and weighed on a cover slip that had been previously pre-weighed. Next, 50 ml of a buffered phosphate solution (pH 6.6) was added. Every five minutes, the cover slip was taken off, and it was weighed for up to thirty minutes. Because of the patch's swelling and water absorption, the weight difference results in an increase in weight.[58]

Swelling increases patch area: A 1x1cm2 drug-loaded patch was cut and placed on a petridish. A graph paper was positioned underneath the petridish to calculate the patch's increased area. 50 ml of pH 6.6 phosphate buffer were added to the petridish. Up to 60 minutes, the patch's length and width elevated every five minutes, and its area was computed. Below represented equation was used to determine the percentage swelling (% S).[59]

$$\% = \frac{Xt - Xo}{Xo} \times 100$$

Where, Xt is the weight or area of the swollen patch after time t.

Xo is the original patch weight or area at zero time

Palatability test: A palatability test is carried out based on the taste after bitterness and its physical appearance. In accordance to the criteria, each batch is referred to as an A, B, or C grade. A formulation is deemed average if it receives a minimum of one A grade. A formulation receiving two A grades is deemed good, and a formulation receiving three A grades is deemed extremely good.[60]

Grades: A = very good, B = good, C = poor.

In vitro drug release: The rotating paddle method described in United States Pharmacopoeia (USP) XXIII is used to examine the drug release rate from bilayered and multilayered tablets. The phosphate buffer with a pH of 6.8 serves as the dissolution medium. The investigation was conducted at 37°C ± 0.5°C and 50 revolutions per minute. The buccal tablet's backing layer membrane was adhered to the glass disk using instant adhesive, specifically cyanoacrylate adhesive. The disk was placed in the dissolution vessel's bottom. Five ml of sample were taken out and replaced with new medium at predefined intervals. The samples were filtered using Whatman filter paper, and after the proper dilution, they were examined using UV spectrophotometry at a suitable nm.[61]

In vitro drug permeation: The in vitro drug permeation study of drugs through the buccal mucosa of sheep or rabbits is carried out at 37°C ± 0.2°C using a Keshary-Chien or Franz type glass diffusion cell. The donor and receptor compartments, where a new buccal mucosa was tied, are included. With the compartments clamped together, the buccal tablet's core side faced the mucosa. Phosphate buffer with a pH of 6.8 is put in the donor compartment, and a pH of 7.4 is put in the receptor compartment. By agitating the receptor compartment at 50 rpm with a magnetic bead, the hydrodynamics condition was preserved. One ml of the sample can be taken out at regular intervals and tested with a UV spectrophotometer at an appropriate nm to determine the drug content.[62]

Stability study in Human saliva: According to ICH guidelines, stability studies of fast dissolving films are conducted for all batches. After a predetermined amount of time, the films were evaluated for disintegration time, drug content, and physical appearance. The stability study of the optimized mucoadhesive patch formulation was performed at 40 °C, 37 ± 5 °C, and 75 ± 5% RH for three months. After three months, the values of all parameters remained the same, with only minor changes in the values of volume entrapment efficiency, percent elongation, and percent drug release after eight hours, which was significant.[63]

Measurement of mechanical properties: In order to test the mechanical properties of the patches, a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK) with a 25 kg load cell and an advanced force gauze based on microprocessor technology was used. A film strip measuring 60 x 10 mm and free of any visible flaws was cut and placed in between two clamps that were 3 cm apart. In order to secure the patch without crushing it during the evaluation, clamps were designed to move at a rate of two ml per second for the upper clamp, pulling apart the strips until the strip broke, while the lower clamp remained stationary. At the moment the strip broke, the force and elongation of the film were recorded. The elongation and tensile strength at break values.[64]

Folding endurance: The method of measuring the folding endurance of the patches involved folding one patch at a time until it broke or up to 300 times by hand, which was deemed sufficient to demonstrate good patch properties. The folding endurance of a patch is measured by the number of times it can be folded in the same way without breaking. Five patches are tested in this manner.[65]

Viscosity: Aqueous solutions made with the same concentration of polymer and plasticizer as the patches. The instrument used is a Brookfield viscometer, model

LVDV-II, mounted on helipath spindle number four. At room temperature, the viscosity was measured at 20 rpm. The recorded values are the average of the three conclusions.[66]

Ageing: Bioadhesive patches were stored in a petri dish lined with aluminium foil in an incubator at 37 ± 0.5 °C and 75 ± 5% RH for six months. Changes in the release behaviour, residence time, appearance, and drug content of the stored patches were assessed after 1, 2, 3, 4, 5, and 6 months. The data represented the mean of three determinations. After 6 months of storage, fresh and aged medicated patches were examined under a scanning electron microscope.[67]

Bioadhesion/Mucoadhesion test

Several Mucoadhesive test methods have been discussed in the literature for studying bioadhesion. These tests are also important during the design and development of a bioadhesive controlled-release system as they ensure compatibility, physical and mechanical stability, surface analysis, and bioadhesive bond strength. The test methods can broadly be classified into two major categories[44,68,69]

1. *In-vitro*/*ex-vivo* methods (Measurement of either tensile or shear stress)

a. Based on measurement of tensile strength.
b. Based on measurement of shear strength
c. Adhesion weight method
d. Fluorescent probe method
e. Flow channel method
f. Mechanical spectroscopic method
g. Falling liquid method
h. Colloidal gold staining method
i. Viscometric method
j. Thumb test
k. Adhesion number
l. Electrical conductance.

2. *In-vivo* methods (Based on the measurement of the residence time of bioadhesive at the application site).

i. Use of radio isotopes
ii. Use of gamma actigraphy.

Review of literature

1. **Ketul Patel *et.al.*, 2023** studious on formulation and evaluation of mucoadhesive buccal tablets loaded nicardipine. The bilayer buccal tablet was made by compressing the medication with the right proportions of polymers. After that, a polymer backing layer is squeezed onto the core tablet. Then the formulated buccal tablets were evaluated by various parameters thickness, hardness, in vitro release. Finally, they concluded that Mucoadhesive tablets helps to overcome nicardipine bioavailability by taking through buccal route.[70]

2. **Senel *et.al.*, 2005**, developed a bioadhesive buccal tablet for nicotine replacement therapy were developed using chitosan and carbomer at different ratios. Magnesium hydroxide was incorporated into the formulations as a pH increasing agent. Then the formulated tablets were evaluated by In vitro release and bioadhesion properties. In vivo studies were carried out in healthy, non-smoker volunteers in comparison to a commercially available transdermal patch. From this investigation they concluded that Release of Nicotine Hydrogen Tartarate from the tablets was increased with the increasing amount of chitosan in formulations, with decrease in the bioadhesion.[71]

3. **Calum R. Park *et.al.*, 2002,** studied on development of Bilayer nicotine mucoadhesive tablets and evaluated to determine the suitability of the formulation as a nicotine replacement product to aid in smoking cessation. The polymer concentration ranges from 0–50% w/w Carbopol 934® and 0–50% w/w hydroxypropyl cellulose (HPC) were used and they tested for adhesive properties and drug release. Mucoadhesion test was carried by using bovine buccal mucosa. Peak detachment force of the tablets was found to reach a maximum at 20% w/w Carbopol 934, and work of adhesion continued with Carbopol 934 concentration. A combination of 20% w/w Carbopol 934 and 20% w/w HPC was thus found to provide suitable adhesion and controlled drug release.[72]

4. **Mahendra kumar *et.al.*, 2021,** discussed on the preparation of metoprolol succinate bio-adhesive buccal tablets by using xanthan gum, guar gum and HPMC as rate-controlling polymers by direct compression techniques. Each formulated three tablets were prepared by using drug and polymers ratios of 1:0.5, 1:0.75, and 1:1. The swelling studies, Surface pH study, mucoadhesion time, bioadhesive strength, In-vitro and ex-vivo drug release studies were performed for 6 hrs for all the formulations. Among all formulations, the optimized candidates were showed controlled and highest drug release. Among all the formulations the preparation contains HPMC (37.5%) shown extended drug release, shown maximum drug release of 100.95±1.58 % and sustained up to 6 hrs selected as an optimized formulation. These results confirmed that suitability of the prepared buccal dosage forms to improve the bioavailability by avoiding the hepatic first-pass metabolism.[73]

5. **Agaiah goud bairi *et.al.*, 2021,** development of mucoadhesive buccal tablets of candesartan cilexetil by using carbopol-934P, hydroxyl propyl methyl cellulose (HPMC), Eudragit RLPO, and sodium carboxy methyl cellulose (Na-CMC) as mucoadhesive polymers. Prepared Candesartan Cilexetil buccal tablet formulations were evaluated for an optimized system based on physicochemical properties, ex-vivo residence time, in-vitro, and ex

vivo permeation studies. the swelling and bio-adhesive time were increased with increasing polymer concentrations. The study concluded that in-vitro release research shown that buccal tablets with sodium carboxy methyl cellulose (Na-CMC) exhibited a higher release than all other formulations. The release mechanism from kinetic methods suggests that the drug release follows zero-order kinetics with a diffusion mechanism. Further, in-vivo research in animal fashions is required to prove the bioavailability performance of the formulation.[74]

CONCLUSION

Oral transmucosal (buccal, sublingual) drug delivery presents a promising alternative because of its simplicity of use and ability to circumvent hepatic metabolism. a substitute for navigating around the restrictions of parental administration and traditional oral medication delivery. In particular, the buccal routes deliver plenty of opportunities, and numerous formulation strategies have been investigated; however, the vast majority of the commercially available formulations at present are only available as tablets and films.

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