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A COMPREHENSIVE REVIEW ON BUCCAL DRUG DELIVERY SYSTEM

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INTRODUCTION

Drug administration through the mucosal membranes (buccal mucosa) is known as buccal drug delivery. It has been introduced in 1947 when dental adhesive powder and gum tragacanth were mixed to apply penicillin to the oral mucosa.[1] Oral route is perhaps the most preferred by patients and clinicians alike among the various routes of drug delivery.[2] Fifty percent (50%) commercially available drugs are administered through oral drug delivery system and this system has more advantages due to ease of administration and patient acceptance.[3] But certain drugs have lack of efficacy due to decreased GI intolerance, bioavailability, unpredictable absorption, pre-systemic elimination etc. In comparison to the conventional oral medications retentive buccal mucoadhesive formulations may prove to be a viable alternative as they can be readily attached to the oral mucosa (Figure 1-2), retained for a longer period of time and can be removed at any time.[4]

Delivery of therapeutic agents via buccal drug delivery system has become highly interesting for both local as well as systemic action. Bio adhesion is the basic process in buccal drug delivery system. Bio adhesion is a phenomenon of interfacial molecular attractive forces between the natural or synthetic polymers and the surfaces of biological substrate which allows the polymer to adhere to mucosal surface for an extended or long period of time.

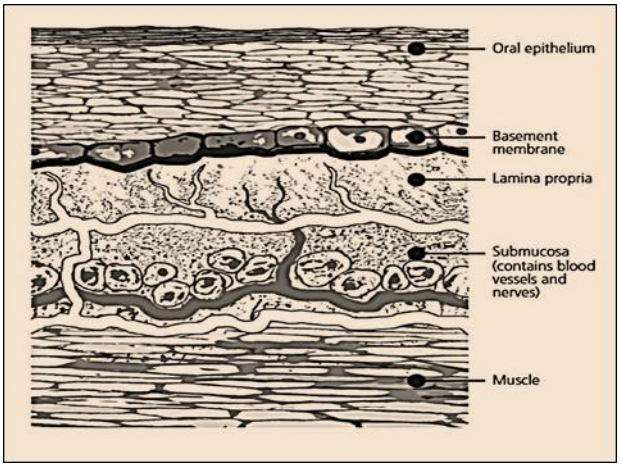


Figure 1: Structure of the Human Oral Mucosa.

IMPORTANCE OF BUCCAL DRUG DELIVERY SYSTEM: Buccal drug delivery is much more recent research subject then the other route for the past several years due to advances of the biotechnology which introduces peptide drugs. These biomolecules cannot be administered by oral route due to low absorption, degradation and low bioavailability. Here, buccal process turns out to be more effective and acceptable. Buccal process is also more effective and acceptable for short half-life drugs (e.g., midazolam) which are not suitable for oral administration due to frequent administration. On the other hand, injectable preparations of short half-life drugs result in poor patient compliance.

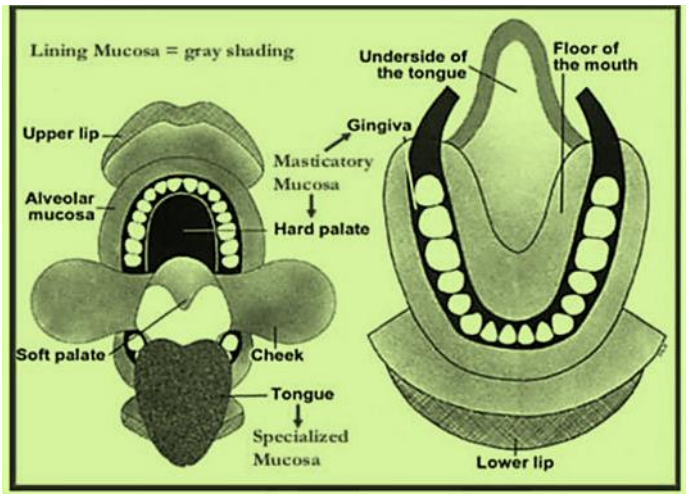


Figure 2: Anatomic Location and Extent of Masticatory, Lining and Specialized Mucosa.

Large surface area represented by buccal mucosa (23% of the total surface of the oral mucosa including the tongue) makes it more fit for systemic drug delivery (Figure 2). The buccal cavity provides a highly vascular mucous membrane site for the administration of drug. In

humans, the permeation of drugs through the buccal epithelium is said to associate both the transcellular and paracellular routes.[5]

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

1. Drug administration is easy and therapy extinction in emergency can be facilitated.
2. Drug can be administered in unconscious and trauma patients. Bioavailability increases due to prevention of first pass metabolism.
3. Flexibility in physical state and flexible shape, size and surface of dosage form. Absorption rate is maximum rate due to close contact with the absorbing membrane. Onset of action is rapid.[6]
4. Mucosal surfaces do not have a stratum corneum in comparison to TDDS. So, the major barrier layer to transdermal drug delivery is not a factor in buccal routes of administration.[7-8]
5. Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
6. Dose reduction can be achieved, reduces dose dependent side effects, and eliminates peak valley profile. Drugs unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered.
7. Improved patient compliance due to elimination of associated pain with injections.[8]

LIMITATIONS OF BUCCAL DRUG ADMINISTRATION

1. Ample dose are often difficult to be administered.
2. Patients have possibility to swallow the tablet being forgotten. Eating and drinking may be restricted till the end of drug release.
3. Unacceptable for drugs, which are unstable at pH of buccal environment.[9]
4. Bitter taste and unpleasant drugs that irritate the mucosa cannot be administered by this route.[10]
5. Continuous saliva secretion from the major and minor salivary glands leads to the rapid dissolution of the drug.[11]
6. Formulation may get disrupted by the swelling and hydration of the bioadhesive polymers due to over hydration of the formation.
7. Surface area available is less for absorption in comparision of oral route.[12]

BUCCAL FORMULATIONS

1. **Buccal mucoadhesive tablets:** Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. Most commonly investigated dosage form tablets are small, flat and oval with a diameter of approximately 5-8 mm. They may be prepared using different methods like as wet granulation technique or direct compression.[13]
2. **Semisolid preparations (Ointments and Gels):** Compared to solid bioadhesive dosage forms bioadhesive gels or ointments have less patient acceptability and most of them are used within the oral cavity only for localized drug therapy. They have the advantage of easy dispersion throughout the oral cavity.[8]
3. **Patches and films:** Patches are mainly laminates consisting of an impermeable backing layer and drug-containing reservoir layer where drug is released in a controlled manner from the drug-containing reservoir layer, and a bioadhesive surface for mucosal attachment.[3] So they consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape.

   A novel mucosal adhesive film called "Zilactin" - consisting of an alcoholic solution of HPC and three organic acids which was applied to the oral mucosal can be retained in place for at least 12 hrs. even when it is challenged with fluids.[8]
4. **Microspheres, microcapsules, micro particles:** They cause less local irritation and provide comfortable sensation of a foreign object within the oral cavity.[3]
5. **Powders:** Powder containing HPC and beclomethasone when sprayed on to the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hrs.[2]
6. **Lozenges:** They act typically within the mouth including the corticosteroids, antimicrobials, local anaesthetics, antifungal and antibiotics.[13]
7. **Bioadhesive liquids and Hollow fibers:** Liquids used to coat buccal surface are viscous and serve as either protective agents or as drug vehicles for delivery of drug on to the mucosal surface. Dry mouth is treated with artificial saliva solution that is retained on mucosal surfaces to provide lubrication. Burnside *et al* designed a micro porous hollow fiber of poysulfone, intended for delivery of histrelin. This fiber is intended to be placed in the buccal cavity for oral mucosal drug delivery.[3]
8. **Buccal sprays:** This type of spray delivers a mist of fine droplets onto mucosal membrane layer. e. g. Estradiol sprays.[10]

PRINCIPAL CONSTITUENTS OF BUCCAL DRUG DELIVERY SYSTEM

1. Drug component: The drug should have following characteristics:

- Small conventional single dose of the drug.
- For controlled drug delivery it should have biological half-life between 2-8 hrs.
- Drug absorption should be passive when given orally.
- Higher t_{max} values when given orally.
- Exhibits first pass effect.

2. Polymers (Bio-adhesive): In the formulation of buccoadhesive dosage forms the first step is to select and characterize the appropriate bio-adhesive polymers. In matrix devices bio-adhesive polymers are also used in which the drug is embedded in the polymer matrix controlling the duration of release of drugs.

3. Backing membrane: Backing membrane material should be inert and impermeable both to the drug and penetration enhancer so that it can prevent the drug loss and offers better patient compliance. Some examples of backing membrane include HPMC, HPC, polycarbophil.

4. Permeation Enhancers: Permeation enhancers are substances facilitating the permeation through buccal mucosa. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients.[14]

MECHANISM OF MUCOADHESION

The adhesion mechanism of certain macro-molecules to the surface of a mucous tissue is not well understood yet. Attraction and repulsion between polymer and mucus membrane are the main forces for mucoadhesion. The attraction force must dominate for a successful mucoadhesion. The mechanism of mucoadhesion is generally divided in two steps: contact stage & consolidation stage. Each step can be facilitated by the nature of the dosage form and its administration process.

From the figure (Figure 3) we can see that the first stage or the contact stage is characterized by the contact between the mucous membrane and the mucoadhesive by means of spreading and swelling of the formu-lation and thus initiating its deep contact with the mucus layer. Again we can see in the consolidation step in presence of moisture the mucoadhe-sive materials are activated.

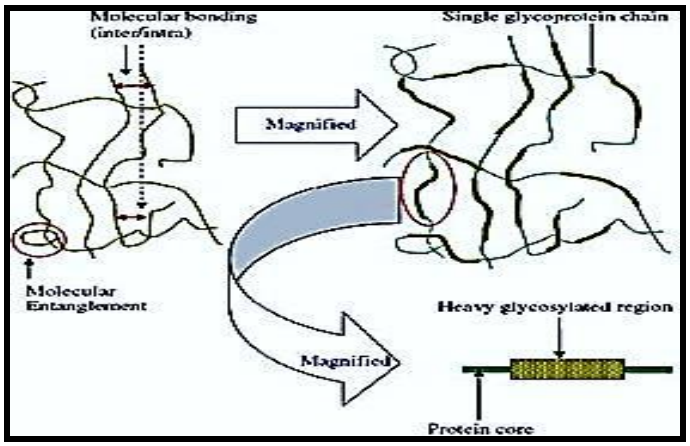


Figure 3: Mechanism of Mucoadhesion.

The mucoadhesive molecules become break free and link up by weak van der Waals and hydrogen bonds in presence of moisture. Different enzymes responsible for hydrolysis like pepsin, trypsin and chymotrypsin, makes the enzymatic activity of buccal mucosa [Carvalho *et al*., 2010]. Different theories about the mucoaddition are as follows:

1. Electronic Theory: According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucus glycoprotein network. This is due to differences in their electronic structure. This proposes to result in the formulation of an electronic double layer at the interface.

2. Adsorption Theory: According to the adsorption theory, adhesive attachment occurs on the basis of hydrogen bonding and Vanderwaal's forces.[15]

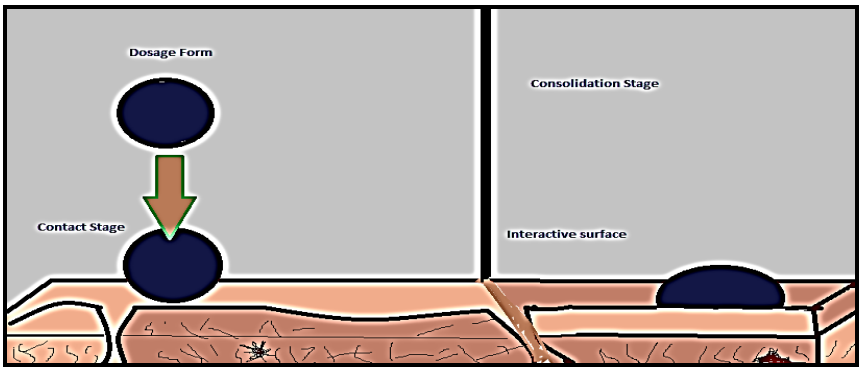


Figure 4: The Process of Consolidation.

According to this theory (figure 4), after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces.[13]

3. Wetting Theory: The wetting theory applies to liquid systems or low viscosity bioadhesives which produce affinity to the surface in order to spread over it. This affinity can

be measured by using measuring techniques for example contact angle which should be equal or close to zero (Figure 5).[11] According to Dupres equation work of adhesion is given by: Wa = YA + YB – YAB

Where A & B refer to the biological membranes and the bioadhesive formulation respectively. The work of cohesion is given by: Wc = 2YA or YB.

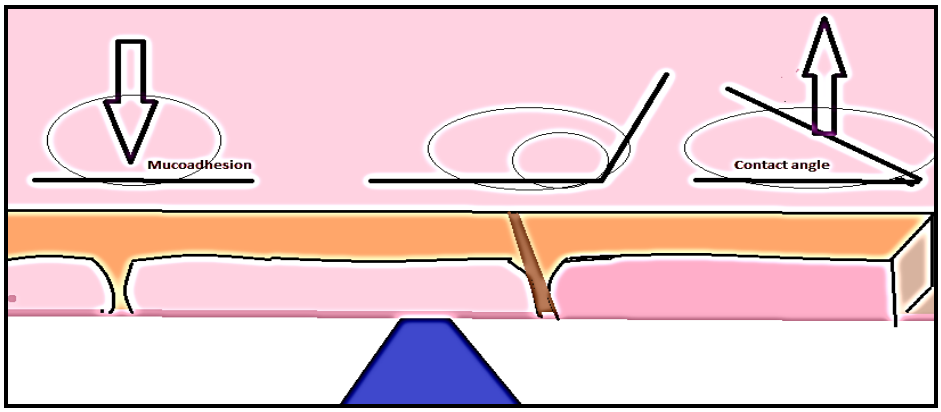


Figure 5: The Wetting Theory.

For a bioadhesive material B spreading on a biologicalsubstrate, the spreading coefficient is given by: SB/A = YA – (YB+YAB) should be positive for a bioadhesive material to adhere to a biological membrane.[16]

4. Diffusion Theory: According to this theory, mucus and the polymer chains mix to a sufficient depth to create an adhesive bond which is semi-permanent type where the penetration depends on diffusion coefficient (Figure 6).

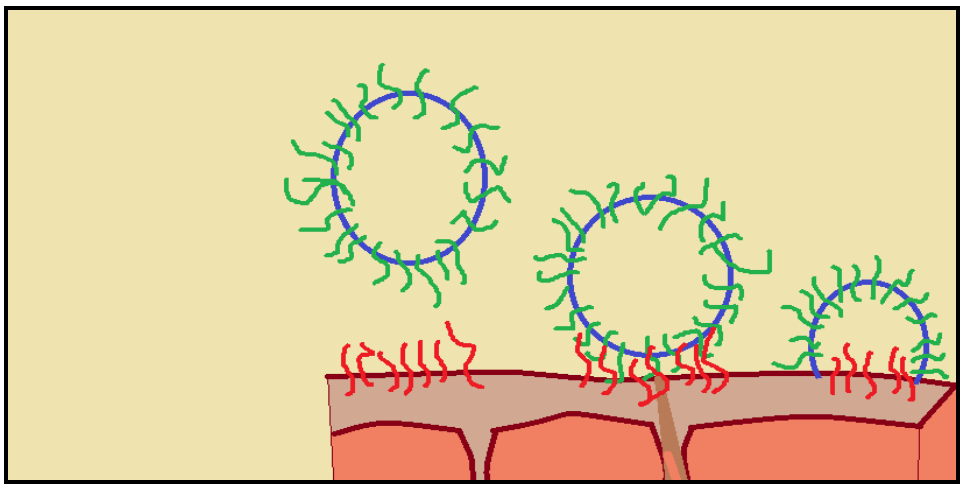


Figure 6: Secondary Interaction between Muco-adhesive device and Mucus.

5. Fracture Theory: Fracture theory of adhesion is related force required to detach or separate two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by, G = (Eε. /L) ½ (Figure 7).

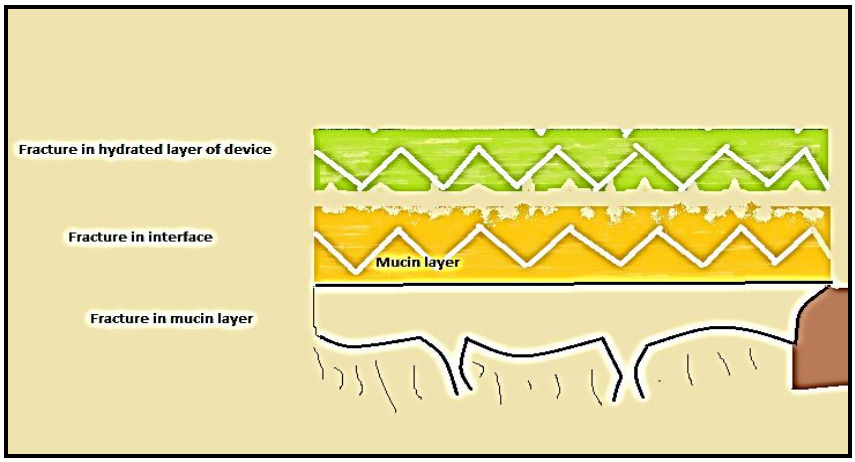


Figure 7: Fractures Occurring for Mucoadhesion.

Where: E- Young's modules of elasticit, ε- Fracture energy, L- Critical crack length when two surfaces are separated.[11]

SOME FACTORS THAT AFFECTS MUCOADHESION IN THE ORAL CAVITY

A. Polymeric Factors

1. **Molecular weight:** In case of linear polymers bio-adhesiveness improves with increasing molecular weight. For maximum mucoadhesion the optimum molecular weight depends upon the tissue and the type of mucoadhesive polymer. Polymer with high molecular weight promotes physical entangling where mucus layer is better penetrated by the low molecular weight polymers. Higher molecular weight polymers will not moisten quickly to expose free groups for interaction with the substrate. On the other hand low molecular weight polymers will dissolve quickly.[17]
2. **Active polymer concentration:** This factor depends on type of dosage form. In case of solid dosage form, the higher the concentration of polymer the stronger the mucoadhesion. However, for liquid dosage form, maximum mucoadhesion is shown when there is an optimum polymer concentration.[18] To produce maximum level of bioadhesion there should be an optimum concentration of a bio adhesive polymer.
3. **Polymer chain flexibility:** It is important for interpenetration and enlargement. The mobility of the individual polymer chain decreases upon cross linking of water soluble

polymers and thus the effective length of the chain decreases that can penetrate into the mucus layer and as a result bioadhesive strength is reduced.

4. **Spatial Conformation:** Spatial confirmation of a molecule is also an important factor. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.
5. **Cross-Linking Density:** As the density of cross-linking increased, diffusion of water into the polymer network occurs at a lower rate which in turn causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin. Flory has reported this general property of polymers, in which the degree of swelling at equilibrium has an opposite relationship with the degree of cross-linking of a polymer.
6. **Hydrogen Bonding Capacity:** It is another critical factor in polymeric mucoadhesion. It was reported that for mucoadhesion to occur, desired polymers must have functional groups and they have to form hydrogen bonds. It was also found that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly vinyl alcohol, hydroxylated methacrylate, and poly methacrylic acid, as well as all their copolymers, have good hydrogen bonding capacity.
7. **Charge sign of polymer:** This is an important element for bioadhesion. In comparison to anionic polymers, nonionic polymers undergo a smaller degree of adhesion. Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. Some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties specially in a neutral or slightly alkaline medium.
8. **Hydration (Swelling):** Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bio adhesion occurs.

B. Environment Related Factors

1. **Applied Strength:** Whatever the polymer the adhesion strength increases with the applied strength or with the duration of its application. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high

pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

2. **pH:** On the surface of both mucus and the polymers pH generally influences the charge. Due to difference in dissociation of functional groups on the amino acids and the carbohydrate moiety of the polypeptide backbone mucus will have a different charge density depending on pH. It should be also noted that pH of the medium is important for the degree of hydration of cross linked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then hydration decreases as the alkalinity increases.
3. **Initial Contact Time:** To determine the extent of swelling and interpenetration of the bioadhesive polymer chains, the initial contact time between the bioadhesive and mucus layer is important. Moreover, bioadhesive strength increases as the initial contact time increases.[17]

C. Physiological Variables

1. **Mucin Turnover:** Mucin turnover is limits the residence time of the mucoadhesive on the mucus layer. Due to mucin turnover mucoadhesives are detached from the surface no matter how high the mucoadhesive strength is. Mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to interact with the mucus layer.
2. **States of disease:** The mucoadhesive property needs to be evaluated if they are used in the diseased state. The physiochemical properties of mucus changes during disease conditions such as bacterial and fungal infections, common cold etc.[8]

MECHANISM OF ABSORPTION BY BUCCAL CAVITY: Absorption of drug through buccal cavity occurs by passive diffusion of the nonionized species through the intercellular spaces of the epithelium using a concentration gradient. By first order kinetics the dynamics of buccal absorption can be explained. There is a linear relationship between time and salivary secretion which can be given as follows:

$-dm/dt = KC/ViVt$

Where, m - mass of drug in mouth at time, K - proportionality constant, C - concentration of drug in mouth at time, Vi - the volume of solution put into mouth cavity and Vt - salivary secretion rate [Reddy *et al*., 2013].

PATHWAYS FOR BUCCAL DRUG ABSORPTION: There is a passive pathway for buccal drug to be transported via oral mucosa (Figure 8).

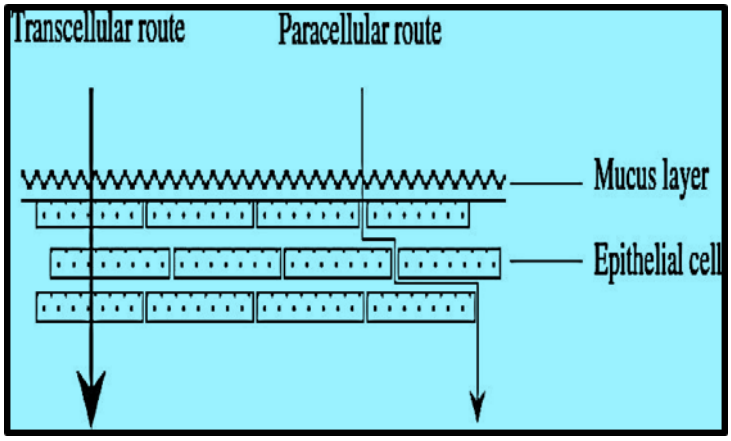


Figure 8: Pathways of Buccul Drug Absorption.

There are two routes: paracellular routes / Intercellular routes and Transcellular routes /Intracellular routes. One route is usually preferred over the other depending on the physicochemical properties of the diffusant. Permeation by the transcellular route may involve transport across the apical cell membrane, intracellular space and basolateral membrane either by passive transport or by active transport. Substances with low molar volume (80 cm^3/mol) can be transported through aqueous pores in cell membranes of epithelium. Cell membrane acts as the major transport barrier for hydrophilic compounds and the intercellular spaces pose as the main barrier to permeation of lipophilic compounds. Due to stratified oral epithelium, solute permeation requires combination of these two routes.[19]

SOME EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES

A. In vitro Methods: In vitro studies uses buccal tissues from animal models examining drug transport across buccal mucosa where animals are sacrificed immediately before the start of an experiment. Firstly buccal mucosa with underlying connective tissue from the oral cavity is surgically removed. After the connective tissue is carefully removed, the buccal mucosal membrane is isolated which are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the in vitro permeation experiments.

B. In vivo Methods: By means of buccal absorption test this method was first originated by Beckett and Triggs (Figure 9).

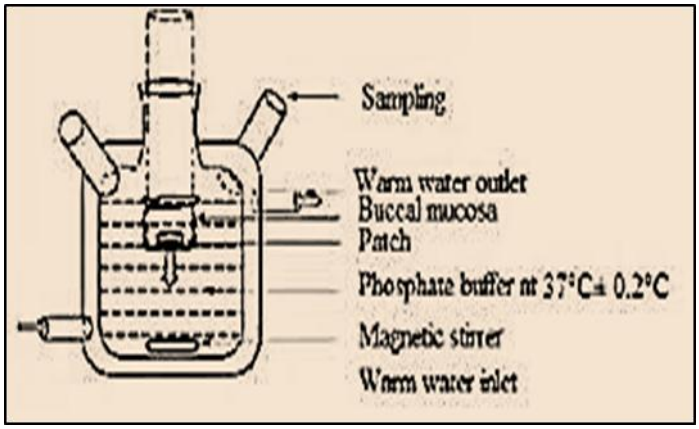


Figure 9: In-vivo Drug Release Apparatus.

The kinetics of drug absorption was measured in this method. Followed by the expulsion of the solution it involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers. In order to assess the amount of drug absorbed the amount of drug remaining in the expelled volume is then determined. Various modifications of the buccal absorption test have been carried out correcting for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization.

C. **Experimental Animal Species**: Another methodology is carried out in experimental Animal Species. Special attention is warranted to the choice of experimental animal species for such experiments aside from the specific methodology employed to study buccal drug absorption/permeation characteristics. Many researchers have also used small animals including rats and hamsters or permeability studies.[14]

BUCCAL PATCHES EVALUATION STUDIES

1. **pH of surface:** To investigate the possibility of any side effects in vivo the surface pH of the buccal patch is determined. Firstly the buccal patches are left to swell by keeping it in contact with 1 ml of distilled water for 2 hr at room temperature on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.[2]
2. **Measurements of thickness:** Using an electronic digital micrometer the thickness of each film is measured at five different locations (centre and four corners).[20]
3. **Folding Endurance:** It is determined manually. Patch is repeatedly folded at same point until it ruptures or breaks. Folding endurance of the patches is determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times manually which

is considered satisfactory to reveal good patch properties. The number of folding required for cracking or breaking a patch was taken as the folding endurance.

4. **Swelling Study:** Due to swelling weight increase. Buccal patches are weighed individually (W1) and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C and examined for any physical changes. A graph paper is placed beneath the petridish, to measure the increase in the area. After every interval of 3 hours, patches are removed from the gel plates and using the filter paper excess surface water is removed carefully. The swollen patches are then again weighed (W2) and using the following formula the swelling index (SI) were calculated.

   SI = {(W2-W1)/W1} X 100

   The difference in the weights gives the weight increase due to absorption of water and swelling of patch.
5. **Study of thermal Analysis:** Using differential scanning calorimeter (DSC) thermal analysis study is performed.
6. **Morphological Characteristics:** Using scanning electron microscope (SEM) morphological characters are studied by.
7. **Test for water absorption capacity:** Circular Patches, with a surface area of 2.3 cm^2 are allowed to swell on the surface of agar plates prepared in simulated saliva and kept in an incubator maintained at 37°C ± 0.5°C. Samples are weighed at various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours) and then allowed to dry for 7 days in a desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded.

Water Uptake (%) = {(Ww – Wf)/ Wf } X 100

Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured.[20]

In Vitro drug release test: Here the dissolution medium consisted of phosphate buffer pH 6.8 maintaining a temperature at 37°C ± 0.5°C and with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material and the disk is allocated to the bottom of the dissolution vessel. Five (5) ml sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UV spectrophotometer.[20]

Ex-Vivo mucodhesion strength test: Fresh buccal mucosa (sheep and rabbit) is collected and used within 2 hours of slaughter and separated by removing underlying fat tissues. The buccal mucosa cut into pieces and a piece is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Before the study two sides of the balance made equal and balanced with a 5g weight. The 5g weight is removed from the left hand side pan which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 10 drops/min to the right-hand side pan until the patch detached from the mucosal surface.[2]

Permeation study: The receptor compartment is filled with phosphate buffer pH 6.8 and is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and then analyzed for drug content.[20]

Ex-vivo mucoadhesion time: The fresh buccal mucosa is tied on the glass slide and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker filled with 200 ml of the phosphate buffer of pH 6.8 kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment and after that patch adhesion is monitored for 12 hours. The time for changes in color, shape, collapsing of the patch and drug content is noted.[2]

8. **Measurement of mechanical properties:** Mechanical properties of the patches can be evaluated using a microprocessor based advanced force gauze equipped with a motorized test. Using a tensile tester mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated. Film strip that has dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip breaks. Force and elongation of the film at the point when the strip breaks is recorded. The tensile strength and elongation at break values are calculated using the formula.

[T= (M X g) / (B X T)]

Where, M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec^2, B - is the breadth of the specimen in cm, T - is the thickness of specimen in cm. Tensile strength (kg/mm^2) is the force at break (kg) per initial cross sectional area of the specimen (mm^2).

9. **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 with age between 18-50 years. In separate petridishes containing 5ml of human saliva buccal patches are placed in a temperature controlled oven at 37°C ± 0.2°C for 6 hours. Films stability study is carried out for all the batches according to ICH guidelines.

Permeability Measurement using animal models: To perform this study the most commonly used animal models are dogs, rabbits, and pigs. A general criterion is the resemblance of the animal mucosa to the oral mucosa of human beings in both ultra-structure and enzyme activity for selecting an in vivo animal model that represent the physical and metabolic barriers of the oral mucosa.[20]

CONCLUSION

Buccal drug delivery offers numerable advantages in terms of administration, accessibility and withdrawal, retentivity, high patient compliance, economy and low enzymatic activity. This system has applications from different angles includes avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. Also this area is well suited for a retentive device and appears to be acceptable to the patient. Another advantage is to accommodate drug permeation the permeability in the local environment of the mucosa can be controlled and manipulated with the right dosage form design and formulation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for noninvasive delivery of potent peptide and protein drug molecules. However, in the area of buccal drug delivery for safe and effective buccal permeation the absorption enhancers are crucial component for a prospective future. Mucoadhesive systems may play an increasing role in the development of new pharmaceuticals with the great influx of new molecules stemming from drug research. Due to success, advantages and ease of access of drug delivery through oral mucosal tissue the buccal and sublingual routes have favourable opportunities and many formulation approaches although the current commercially available formulation are mostly limited to tablets and films. So it can be said that the buccal mucosa offers several advantages for controlled drug delivery for long period of time and also favourable area for systemic

delivery of orally unsatisfactory drugs and attractive alternative for non-offensive delivery of potent peptide and protein drug molecule. For improving drug absorption especially for the new generation oral mucoadhesive dosage forms will be an exciting research in coming days.

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