CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3601257

Available online at: http://www.iajps.com *Review Article*

APPROACHES OF BUCCAL DRUG DELIVERY SYSTEM

[1]K. Malleswari*, [2]D.Rama Brahma Reddy, [3]D. Anil Reddy

[1]Department of Pharmaceutics, Nalanda institute of Pharmaceutical sciences, Kantepudi, Guntur.
Email:Malleswarirao24@gmail.com

Article Received: November 2019 **Accepted:** December 2019 **Published:** January 2020

Abstract:

Buccal drug delivery leads direct access to the systemic circulation through the internal jugular vein by passes drugs from the hepatic first pass metabolism leading to high bioavailability. Buccal route is an attractive route of administration for systemic drug delivery. Buccal bio adhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases. This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

Keywords: *buccal drug delivery system, film, bioadhesive.*

Corresponding author:

K.Malleswari,

Associate Professor, Nalanda institute of Pharmaceutical Sciences Siddharth nagar,katepudi(v),sattenapalli (M), Guntur Dist-522438, Andhra Pradesh, Ph:8499038636, Email:malleswarirao24@gmail.com

QR code

Please cite this article in press K. Malleswari et al., ***Approaches Of Buccal Drug Delivery System.,*** *Indo Am. J. P. Sci, 2020; 07(01).*

INTRODUCTION:

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption. Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity). Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion.[1]

The use of mucoadhesive polymers in buccal dru g delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.[2]

POTENTIAL BENEFITS OF BUCCAL FILMS:

- Buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient.
- No need of chewing and swallowing.
- No risk of chocking.
- The film increases the systemic bioavailability of the drugs, as it bypasses the Hepatic first pass metabolism.
- Drug can be protected from degradation by GI enzymes and the acidic
- Environment.
- Rapid onset of action and minimum side effects.
- Self administration is possible.
- Accurate dosing compared to liquid dosage forms.
- Taste masking is possible.
- Prolongs the residence time of the dosage form at the site of absorption, hence Increases the bioavailability.
- Ease of administration to pediatric, geriatric patients, and also to the patient Who are Mentally retarded, disabled or non-cooperative.

Limitations in buccal patches:

- The area of absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.
- The area of absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.
- Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane.[3]
- Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.
- Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route.
- Conventional type of buccal drug delivery systems did not allow the patient to concurrently eat, drink or in some cases, talk.[4]

Anatomy and Physiology of Oral Mucosa:

Oral mucosal region is adhesive in nature and acts as a lubricant, allowing the cells to move relative to one another with less friction. Four sites namely buccal cavity, the lingual area, the palate and gingival region have been used for drug administration. The most commonly used site for drug administration of the four sites mentioned above is the buccal route. The anatomic site for drug administration between the cheek and gingival is known as the buccal mucosa. The oral mucosa is composed of three layers. The first layer is the stratified squamous epithelium, underneath this layer lays the basement membrane. The basement membrane overlies the lamina propria and submucosa. The constitution of the epithelium within the different sites of the oral cavity shows dissimilarity. The epithelium in the soft palate, buccal and sublingual area is not keratinized, therefore not containing ceramides and acylceramidesm which are associated with providing a barrier function. The mucosa of the buccal and sublingual region have only small amounts of ceramidem and is thus more permeable when compared to other regions of the oral cavity.[6]

A layer of mucus is present on the surface of the epithelial layer of cells. This plays a major role in cell-to-cell adhesion, oral lubrication, as well as mucoadhesion of mucoadhesive drug delivery systems. The buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of a retentive system. For buccal drug delivery, adhesion to the oral mucosa permits not only the intimacy of contact and the possibility of improved drug absorption, but also the ability to achieve an optimum residence time at the site of administration[7] . These characteristics make the buccal mucosa as a more appropriate site for prolonged systemic delivery of drugs Figures 1 ,2 and 3.

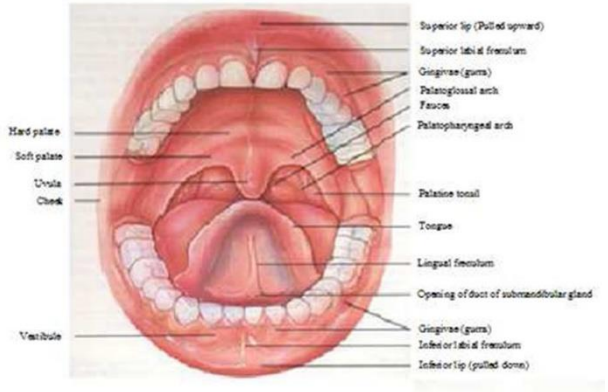


Figure 1: Anatomical structure of Oral Cavity (Anterior View)

Components or structural features of oral cavity (Figure 1):

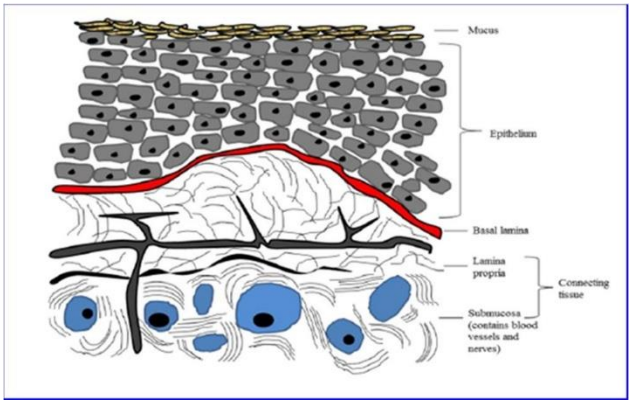


Figure no:2 structure of buccal mucosa

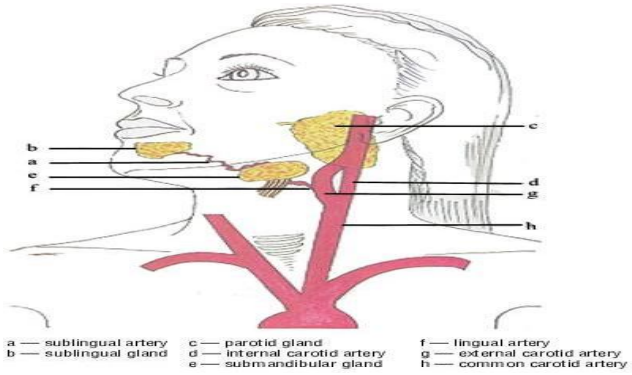


Figure no: 3 Absorption through oral mucosa

Oral mucosal sites:
Within the oral mucosal cavity,delivery of drugs is classified in to three categories-

1. Sublingual delivery:
The administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tounge and the floor of the mouth to the systemic circulation.

2. Buccal delivery:
It is the administration of drug via the buccal mucosa(the lining of the cheek)to the systemic circulation

3. Local delivery:
The treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease.

- These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions.
- Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).
- Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate.
- The tongue projects from the floor of the cavity

Physiological aspects and functions of oral cavity (Figure 2):

- As a portal for intake of food material and water.
- Helps in chewing, mastication and mixing of food stuff.
- Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- To aid in speech and breathing process.

Buccal absorption:
Buccal absorption leads systemic or local action via buccal mucosa.

Mechanism of buccal absorption:
Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed.[8]The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal

absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows .

$$- dm/dt = Kc/ViVt$$

Where,
M - Mass of drug in mouth at time ıtı
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

Formulation aspects of buccal films:

Active pharmaceutical ingredient [APIs]

Generally 5% w/w to 30% w/w of active pharmaceutical ingredients can be incorporated in the buccal film. Water soluble APIs are present in the dissolved state in the buccal film or in the solid solution form. The water insoluble drugs are dispersed uniformly in the film. This involves the distribution of water insoluble molecules in water miscible polymer, or the solubility of the drug can be enhanced by complexation with various cyclodextrins. Depending upon the desired release profile, APIs can also be added as milled, micronized, or in the form of nano crystals or particles. The use of micronized API will improve the texture of the film and also for better dissolution and uniformity in the buccal film.[9] The buccal films are more advantageous in certain clinical situations where instantaneous release of the medicaments is necessary for prompt relief. Some of such type of clinical situations includes cough, allergy, motion sickness, pain and other local oral manifestations.

Mucoadhesive polymers:

Polymers with different characteristics have to be considered depending on the type of formulation. Different situations for buccal mucoadhesion are possible depending on the dosage form. Mucoadhesive polymers are classified into two main groups, such as hydrophilic polymers and hydrogels. The hydrophilic polymers most commonly used in buccal dry or partially hydrated dosage forms include polyvinyl alcohol [PVA], sodium carboxy methylcellulose [NaCMC], hydroxyl propyl methyl cellulose [HPMC], hydroxyl ethyl cellulose and hydroxypropyl cellulose [HPC].[10] Hydrogels include anionic polymers like carbopol, polyacrylates, cationic polymers like chitosan and non ionic polymers like eudragit analogues.

Plasticizers:

Typically, the plasticizers are used in the concentration of 0-20% w/w of dry polymer. Plasticizer is an important ingredient of the film, which improves the flexibility of the film and reduces the bitterness of the film by reducing the glass transition temperature of the film. The selection of plasticizer depends upon the compatibility with the polymer and type of solvent employed in the casting of film. Plasticizers should be carefully selected because improper use of the plasticizers affects the mechanical properties of the film. PEG 400, Propylene glycol, Glycerol, castor oil is most commonly used plasticizers.[11]

Penetration enhancers:

Penetration enhancers are also the important excipients to be added in the buccal film formulation. These are required when a drug has to reach the systemic circulation to exert its action. These must be nonirritant and have a reversible effect. The epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of buccal penetration enhancers include fatty acids that act by disrupting intercellular lipid packing, surfactants, bile salts, and alcohols.[12]

Taste masking agents:

Taste masking agents or taste masking methods should be used in the formulation if the APIs have bitter taste, as the bitter drugs makes the formulation unpalatable, especially for pediatric preparations. Thus, before incorporating the API in the buccal film, the taste needs to be masked.[13] Various methods can be used to improve the palatability of the formulation, such as complexation technology, salting out technology, etc.

Sweetening agents:

Sweeteners have become the important excipients for oral disintegrating drug delivery system. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners, as well as artificial sweeteners, are used to improve the palatability of the mouth dissolving formulations. The natural sweeteners include sucrose, dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose.[14] Artificial sweeteners should be used if the dosage form is meant for diabetic patients. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners, followed by acesulfame-K, sucralose, alitame and neotame, which come under the second generation artificial sweeteners.

Saliva stimulating agent:
Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving film formulations. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6% w/w of weight of the film.[15]

Flavoring agents:
The flavoring agents are very important in case of oral dissolving systems. The acceptance of the oral disintegrating formulation by a patient depends on the initial flavor quality, which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils, while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. Flavors can be used alone or in the combination.[16] The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferably, up to 10% w/w flavors are added in the buccal film formulations. To improve the flavor strength and to enhance the mouth-feel effect of the product, cooling agents like monomethyl succinate can be added.

Coloring agents:
To improve the elegant appearance of films, coloring agents are incorporated in the formulation. FD&C approved coloring agents are used .[17]

Manufacturing Methods:
The buccal film manufacturing process includes the following techniques.

1. Solvent casting technique
2. Hot melt extrusion technique

1. Solvent casting method
The solvent casting method is widely preferred for the manufacture of buccal films. This process involves the following steps:

- Water soluble ingredients (polymers) are dissolved in water to form homogenous viscous solution.
- API and other excipients are dissolved in suitable solvent to form a clear viscous solution.
- Both the solutions are mixed and the resulting solution is casted as a film and allowed to dry.

2. Hot melt extrusion technique
Hot melt extruder is used in this process. This technique involves shaping a polymer into a film via the heating process. A blend of pharmaceutical ingredients including API in dry state is filled in the hopper, conveyed, mixed and subjected to the heating process, and then extruded out in molten state melted by the extruder. The molten mass thus formed is used to cast the film. A critical step is the casting and drying process. This technique has many advantages, such as this process involves lower temperature and shorter residence times of the drug carrier mix, absences of organic solvents, continuous operation.

Evaluation of Buccal Films:
The buccal films are evaluated by

Weight and thickness of the film:
For evaluation of film weight, three films of every formulation are taken and weighed individually on a digital balance. The average weights are calculated. Similarly, three films of each formulation were taken and the film thickness is to be measured using micrometer screw gauge at three different places, and the mean value is to be calculated .[20]

Surface pH of films:
For determination of surface pH, three films of each formulation are allowed to swell for 2 h on the surface of an agar plate. The surface pH is to be measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings is to be recorded .[21]

Swelling index:
After determination of the original film weight and diameter, the samples are allowed to swell on the surface of agar plate kept in an incubator maintained at 37 ± 0.2ºC. Weight of the films (n=3) is determined at different time intervals (1-5 h). The percent swelling, % S is to be calculated using the following equation:
Percent swelling [% S]=[Xt–Xo/Xo]×100,
Where, Xt=The weight of the swollen film after time t, x Xo=The initial film weight at zero time.[22]

Folding endurance:
Three films of each formulation of required size are cut by using sharp blade. Folding endurance is to be determined by repeatedly folding the film at the same place, till it is broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance .[23]

Moisture content:
The prepared films are to be weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are to be weighed again after a specified interval, until they show a constant weight. The percent moisture content is to be calculated by using following formula .[24]

% Moisture content=[Initial weight–Final weight/Final weight]×100

Moisture uptake:
Weighed films are kept in desiccators at room temperature for 24 h.

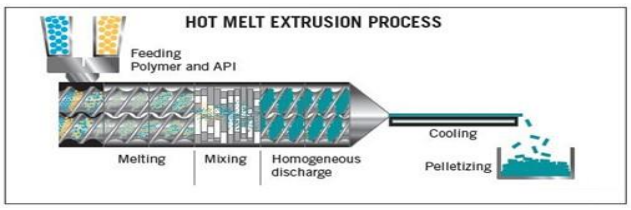


Figure 4: Hot melt extrusion process.

These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators, until a constant weight is achieved. % moisture uptake is calculated as given below.
% Moisture uptake=[Final weight–Initial weight/Initial weight]×100

In-vitro residence time:
The *in vitro* residence time is determined using IP disintegration apparatus using 900 mL of the disintegration medium maintaining at 37 ± 2°C. The segments of rat intestinal mucosa, each of 3 cm length, are to be glued to the surface of a glass slab, which is then vertically attached to the apparatus. Three mucoadhesive films of each formulation are hydrated on one surface and the hydrated surface is brought into contact with the mucosal membrane. The glass slab is vertically fixed to the apparatus and allowed to move up and down.[25] The film is completely immersed in the buffer solution at the lowest point, and is out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface is to Drug content uniformity.

Three film units (each of 20 mm diameter) of each formulation has to be taken in separate 100 mL volumetric flasks, 100 mL of solvent has to be added and continuously stirred for 24 h. The solutions have to be filtered, diluted suitably and analyzed at specified nm in UV spectrophotometer. The average of drug contents of three films has to be taken as final reading.

Surface characterization studies:
The scanning electron photomicrograph of the film is taken at 6000 X magnification. The prepared film containing drug is examined for clear and colorless surface. The photomicrographs of the film with the drug and the blank film are compared, and are examined whether the drug is distributed uniformly throughout the film in an amorphous form .[26]

In-vitro dissolution studies:
Dissolution studies are carried out for all the formulations, employing USP dissolution apparatus at 37 ± 0.5ºC, rotated at constant speed of 50 rpm using 900 mL of dissolution medium. A sample of drug film is used in each test. An aliquot of the sample is periodically withdrawn at suitable time interval and the volume is replaced with fresh dissolution medium. The sample is analyzed spectrophotometrically at specified nm .[27]

Organoleptic evaluation:
The prepared buccal film should possess the desired features of sweetness and flavor, which is acceptable to a large mass of population. Controlled human taste panels are used for psychophysical evaluation of the product. *In-vitro* methods of utilizing taste sensors, specially designed electronic tongue measurement devices can be used for this purpose .[28]

Packaging:
Many options are available for buccal films packing, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roller dispenser. Single packaging is mandatory for films. An aluminium pouch is the most commonly used packaging system. There are some patented packaging

systems for oral films. Labtec company has patented packaging technology called Rapid card and Amcor Flexibilities Company has patented Core-peel technology.

Ex–vivo Permeation Studies:
The modified Franz diffusion cell is used for permeation studies. It consists of two compartments, one is donor compartment and another is receptor compartment of 18 mL capacity and having 0.785 cm2 effective diffusion area. The receptor compartment was covered with water jacket to maintain 37°C.

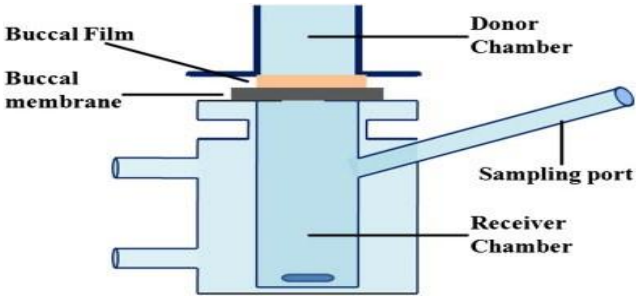
The porcine or rabbit buccal mucosa can be used for these studies. The buccal mucosa is carefully separated from fat and muscles using scalpel. The buccal epithelium is isolated from the underlying tissue. The buccal epithelium was used within 2 hrs upon removal. The separated buccal epithelium is mounted between two chambers and receptor chamber is filled with PBS pH 7.4. The buccal epithelium is allowed to stabilize for the period of 1 hr. After stabilization of buccal epithelium, the film is kept on buccal epithelium and periodically samples are withdrawn and some fresh volume is replaced. The aliquots are analyzed spectrophotometrically .[29]

Flexibility in Formualtion of Buccal Films:
There is wide range of flexibility in developing the buccal films. The main benefits of buccal film formulation includes that many of the eligible Active pharmaceutical ingredients (API's) can be formulated as buccal films and many of the physical properties can be altered, such as material composition, film dissolution rates and API absorption rates. The formulation of buccal films includes film forming polymers and other additives. Formulators can design the films to release the drug immediately in seconds as immediate drug release formulations, or to deliver the dose over a period of hours as controlled release formulations by modifying the combination of film-forming polymers and film thickness. The buccal mucosal area, as it has an expanse of smooth and relatively immobile surface, the area is well suited for placement of a retentive device and appears to be acceptable to the patient. The anatomical features of buccal mucosa make it as an appropriate site for prolonged systemic delivery of drugs. The buccal mucosa permits not only the intimacy of contact and the possibility of improved drug absorption, but also the ability to achieve an optimum residence time at the site of administration.[30] Buccal film formulation is more feasible drug delivery method even for the systemic delivery of orally inefficient drugs, and it as an attractive alternative for the delivery of protein and peptide drug molecules.

Applications

- Multilayer drug film construction is possible, which an emerging area for immediate application. Two or more drugs could be combined into one format and the layers may be formulated to have the same or various dissolution rates.
- The films can be formulated in such a way that the dissolution rates of the drugs can range from minutes to hours.
- Films acts as gastro retentive dosage forms, in which the dissolution of the films could be triggered by the pH or enzyme secretions of gastro intestinal tract, and could be potentially used to treat gastro intestinal disorders.

Figure 5: Franz diffusion cell.



CONCLUSION:
The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be

acceptable to the patient. 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 non-invasive delivery of potent peptide and protein drug molecules. the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

REFERENCE:

1. Giradkar KP, et al, Design development and *in vitro* evaluation of bioadhesive dosage form for buccal route, International journal of pharma research & development, 2010, 2(4).
2. Shidhaye SS, et al, Mucoadhesive bilayered patches for administration of sumatriptan, AAPS pharm sci tech, 2009, 9(3).
3. Zhang.J et al, An In Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation Barrier after Exposure to Permeation Enhancers Apparent Evidence of Effective Enhancement without Tissue Damage, Int. J. Pharm, 1994, 101, 15–22.
4. Shojaei Amir H, Buccal Mucosa As A Route For Systemic Drug Delivery: A Review;J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 1998;1 (1):15-30.
5. Sevda Senel, Mary Kremer, Katalin Nagy and Christopher Squier, Delivery of Bioactive Peptides and Proteins Across Oral (Buccal) Mucosa, Current Pharmaceutical Biotechnology, 2001; 2: 175-186.
6. Amir H, et al, Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology, 2001, 127. 4.
7. Pramodkumar TM et al, Oral transmucosal drug delivery systems, Indian drug, 2004, 41(2), 63-1. 8)Edsman K, et al, Pharmaceutical applications of mucoadhesion for the non-oral routes, Journal of pharmacy & pharmacology, 2005, 57, 3-19.
8. Steward A et al, The Effect of Enhancers on the Buccal Absorption of Hybrid (BDBB) Alpha
9. Interferon, Int. J. Pharm, 104, 1994, 145–149.
10. Aungst BJ and Rogers NJ, Site Dependence of Absorption- Promoting Actions of Laureth9, Na Salicylate, Na2EDTA, and Aprotinin on Rectal, Nasal, and Buccal Insulin Delivery, Pharm. Res, 1988, 5 (5), 305–308.
11. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR, et al. (2004) Development and evaluation of buccoadhesive propranolol hydrochloride table formulations: Effect of fillers. Farmaco 59: 155-161.
12. Remunan-Lopez C, Portero A, Vila-Jato JL, Alonso MJ (1998) Design and evaluation of chitosan/ethyl cellulose mucoadhesivebilayered devices for buccal drug delivery. J Control Release 55: 143-152.
13. Rathborne M, Drummond B, Tucker I (1994) Oral cavity as a site for Systemic drug delivery. Adv Drug Deliv Rev 13: 1-22.
14. Hao J, Heng PWS (2003) Buccal delivery systems. Drug Dev lnd Pharm 29: 821-832.
15. Kurosaki Y, Kimura T (2000) Regional variation in oral mucosal drug permeability. Crit Rev Ther Drug Carrier Syst 17: 467-508.
16. Lee JW, Park JH, Robinson JR (2000) Bioadhesive-based dosage forms: the next generation. J Pharm Sci 89: 850-866.
17. Veuillez F, Kalia YN, Jacques J, Deshusses, Buri P (2001) Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm 51: 93-109.
18. Sudhakar Y, Kuotsu K, Bandyopadhyay AK (2006) Buccalbioadhesive drug delivery- a promising option for orally less effective drug. J Control Release 114: 15-40.
19. Joseph RR, Vincent K L (1987) Lee controlled drug delivery. (2ndEdn), MarcelDekkerinc, New York, USA 42-43.
20. Pfister WR, Ghosh TK (2005) Drug delivery to the oral cavitymolecules to market. Marcel Dekker, New York, USA.
21. Bhura N, Sanghvi K, Patel U, Parmar B, Patel D (2012) A review on fast dissolving film. IJPRBS 1: 66-89.
22. RathaAdhikari SN, Nayak BS, Nayak AK, Mohanty B (2010) Formulation and evaluation of buccal patches for delivery of atenolol. AAPS Pharm Sci Tech 11: 1038-1044.
23. Donnelly R, McCarron P, Tunney M, Woolfson A (2007) Potential of photodynamic therapy in treatment of fungal infections of the mouth. Design and characterisation of a mucoadhesive patch containing toluidine blue O. J Photochem Photobiol B 86: 59-69.
24. Khanna R, Agarwal SP, Ahuja A (1997) Preparation and evaluation of mucoadhesivebuccal films of clotrimazole for oral Candida infections. Indian J Pharm Sci 59: 299-305.
25. Repka M, Prodduturi S, Stodghill S (2003) Production and characterization of hot melt extruded films containing clotrimazole. Drug Dev Ind Pharm 29: 757-765.
26. Senel S, Ikinci G, Kas S, Yousefi-Rad A, Sargon M, et al. (2000) Chitosan films and hydrogels of

chlorhexidinegluconate for oral mucosal delivery. Int J Pharm 193: 197-203.
27. Singh S, Jain S, Muthu MS, Tiwari S, Tilak R (2008) Preparation and evaluation of buccalbioadhesive films containing clotrimazole. AAPS Pharm Sci Technol 9: 660-667.
28. Danckwerts MP (2003) Intraoral drug delivery: A comparative review. Am J Drug Deliv 1: 149-224.
29. quier CA (1991) The permeability of oral mucosa. Crit Rev Oral Biol Med 2: 13-32
30. Shojaei AH (1998) Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Sci 1: 15-30.
31. PapolaVibhooti, Kothiyalpreeti (20013) Wafers Technology-A newer approach to smart drug delivery system. Ind J Res Pharm Biotechnol 1.