Review Article

Buccal Mucosa: A Novelistic Route of Drug Delivery

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ABSTRACT

The buccal mucosa has been investigated for local drug therapy & systemic drug delivery of therapeutic drugs that are subjected to first pass metabolism or are unsuitable with in the G.I.T. Among the various trance mucosal routes the buccal mucosa is very suitable for bioadhesion system because of excellent accessibility, an expanse of smooth muscles & relative immobile mucosa, hence suitable for drugs with a short half life, requiring a sustained released effect, sensitive to enzymatic degradation or poor solubility may be good candidates to deliver via the oral cavity.The buccal mucosa provides the direct entry in to systemic circulation. These data support by the fact that the thickness between epithelium and submucosa of buccal cavity is 594µm. The release of the drug can be affected by continuous secretion of saliva.On the other hand, the buccal route is characterized by some intrinsic limitations (barrier properties of the mucosa, small area available for drug absorption, short residence time of the formulation caused by physiologic-removal mechanisms), which have to be considered in the design of buccal drug delivery systems. To overcome this drawback several mucoadhesive dosage forms are used. This article deals with various prospects of buccal drug delivery by discussing anatomy & physiology of buccal route, path of drug absorption, permeability & various formulations for buccal drug delivery along with current advancement including protein and peptide drug delivery through this so effective drug delivery route.

Keywords: Anatomy & Physiology; Buccal Mucosa; Formulation aspects; Permeability.

INTRODUCTION

Buccal mucosa

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. 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[1-3]. 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[4].Though the nasal rectal,vaginal, and ocular mucosae all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration[1-7].

The oral cavity, on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage[8-10] and the virtual lack of Langerhans cells[11]makes the oral mucosa tolerant to potential allergens. Furthermore, oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

(i) Sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth,

(ii) Buccal delivery, which is drug administration through the

mucosal membranes lining the cheeks (buccal mucosa), and

(iii) Local delivery, which is drug delivery into the oral cavity.

The buccal region offers an attractive route of administration for systemic drug delivery. The Buccal mucosa has a rich blood supply and it is relatively permeable.

Advantages of Buccal Drug Delivery System[12-18]: Drug administration via buccal mucosa offers several distinct advantages:

1. The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.
2. Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.
3. Easy access to the membrane sites so that the delivery system can be applied, localized and removed easily.
4. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
5. High patient acceptance compared to other non-oral routes of drug administration.
6. Tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers.
7. Increased residence time combined with controlled API release may lead to lower administration frequency.
8. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
9. As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.
10. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal drug delivery.
11. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.
12. Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents etc.
13. It allows the local modification of tissue permeability, inhibition of protease activity and reduction in immunogenic response. Thus, delivery of therapeutic agents like peptides, proteins and ionized species can be done easily.

Challenges for Buccal Drug Delivery System[19-20]: The main challenges of buccal administration are:

1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including buccal membrane.
2. Barrier properties of the mucosa.
3. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
4. The hazard of choking by involuntarily swallowing the delivery system is a concern.
5. SalivaSwallowing can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

ANATOMY & PHYSIOLOGY OF BUCCAL MUCOSA

Structure

The oral mucosa is composed of an outermost layer ofstratified squamous epithelium (Figure 1). Below thislies a basement membrane, a lamina propria followedby the submucosa as the innermost layer. Theepithelium is similar to stratified squamous epitheliafound in the rest of the body in that it has a mitoticallyactive basal cell layer, advancing through a number ofdifferentiating intermediate layers to the

superficiallayers, where cells are shed from the surface of theepithelium[21]. The epithelium of the buccal mucosais about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. Theepithelial cells increase in size and become flatter asthey travel from the basal layers to the superficiallayers.

The turnover time for the buccal epithelium has beenestimated at 5-6 days[22], and this is probablyrepresentative of the oral mucosa as a whole. The oralmucosal thickness varies depending on the site: thebuccal mucosa measures at 500-800 µm, while themucosal thickness of the hard and soft palates, thefloor of the mouth, the ventral tongue, and the gingivaemeasure at about 100-200 µm. The composition of theepithelium also varies depending on the site in the oralcavity. The mucosae of areas subject to mechanicalstress (the gingivae and hard palate) are keratinizedsimilar to the epidermis. The mucosae of the softpalate, the sublingual, and the buccal regions,however, are not keratinized[22]. The keratinized epithelia contain neutral lipids like ceramides andacylceramides which have been associated with thebarrier function. These epithelia are relativelyimpermeable to water. In contrast, non-keratinizedepithelia, such as the floor of the mouth and the buccalepithelia do not contain acylceramides and only havesmall amounts of ceramide[23-25]. They also containsmall amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. Theseepithelia have been found to be considerably morepermeable to water than keratinized epithelia[22-24].

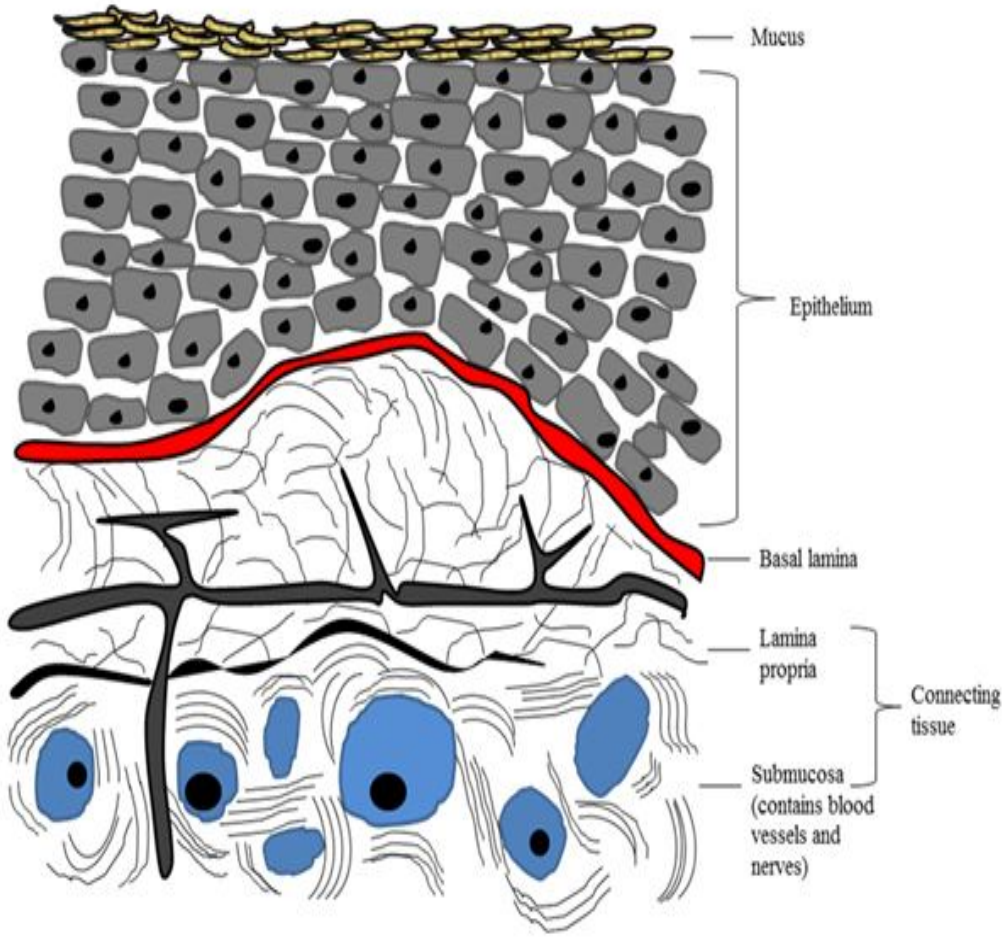

Fig. 1: Structure of oral mucosa

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin[26]. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal and buccal greater than palatal[22]. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG)[27]. When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase[28] and lanthanum nitrate[29]. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium.

The components of the MCGs in keratinized and non-keratinized epithelia are different, however[23]. The MCGs of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other nonpolar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids[23].

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another[30]. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems[31]. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa; mucus is secreted by the major and minor salivary glands as part of saliva[30, 32]. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands[30, 32]. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer[21].

Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralisation of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries[33]. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation[30, 32]. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as

vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.
The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva[34].

Role of Saliva[34]

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

Role of Mucus[34]

- Made up of proteins and carbohydrates.
- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery systems

Buccal Routes of Drug Absorption

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes.

Buccal Mucosa as a Site for Drug Delivery

As stated above in section I, there are three different categories of drug delivery within the oral cavity (i.e., sublingual, buccal, and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted[22]. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailabilities seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches[35], periodontal disease[36-37], bacterial and fungal infections[38], aphthous and dental stomatitis[39], and in facilitating tooth movement with prostaglandins[40].
The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic transmucosal drug delivery[22, 27].First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery. Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less

permeable molecules, and perhaps peptide drugs.

Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa (Table 1). Since the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosae have been shown to work in improving buccal drug penetration[41]. Drugs investigated for buccal delivery using various permeation/absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol[42], ionizable low molecular weight drugs such as acyclovir[43-44], propranolol[45], and salicylic acid[46], large molecular weight hydrophilic polymers such as dextrans[47], and a variety of peptides including octreotide[48], leutinizing hormone releasing hormone (LHRH)[49], insulin[41], and a-interferon[50] have all been studied.

A series of studies[47,51-52] on buccal permeation of buserelin and fluorescein isothiocyanate (FITC) labelled dextrans reported the enhancing effects of di- and tri-hydroxy bile salts on buccal penetration. Their results showed that in the presence of the bile salts, the permeability of porcine buccal mucosa to FITC increased by a 100-200 fold compared to FITC alone. The mechanism of penetration enhancement of FITC-labelled dextrans by sodium glycocholate (SGC) was shown to be concentration dependent[52]. Below 10 mM SGC, buccal permeation was increased by increasing the intercellular transport and at 10 mM and higher concentrations by opening up a transcellular route. Gandhi and Robinson[46] investigated the mechanisms of penetration enhancement of transbuccal delivery of salicylic acid. They used sodium deoxycholate and sodium lauryl sulfate as penetration enhancers, both of which were found to increase the permeability of salicylic acid across rabbit buccal mucosa. Their results also supported that the superficial layers and protein domain of the epithelium may be responsible for maintaining the barrier function of the buccal mucosa.

Table 1: List of permeation enhancers[4]

S. no	Permeation Enhancers	Sr. no	Permeation Enhancers
1	2,3-Lauryl ether	13	Phosphatidylcholine
2	Aprotinin	14	Polyoxyethylene
3	Azone	15	Polysorbate 80
4	Benzalkonium chloride	16	Polyoxyethylene
5	Cetylpyridinium chloride	17	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	18	Sodium EDTA
7	Cyclodextrin	19	Sodium glycocholate
8	Dextran sulfate	20	Sodium glycodeoxycholate
9	Glycol	21	Sodium lauryl sulfate
10	Lauric acid	22	Sodium salicylate
11	Lauric acid/Propylene	23	Sodium taurocholate
12	Lysophosphatidylcholine	24	Sodium taurodeoxycholate

FORMULATION ASPECTS & DOSAGE FORMS FOR BUCCAL DRUG DELIVERY

Over the past few years, different dosage forms intended for buccal drug delivery have been developed[53].

Buccal mucoadhesive dosage forms can be categorized into three types:

Type I- It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II- In this type, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer,

creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

Type III- This is a unidirectional release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa. Buccal dosage forms can also be classified as either a “reservoir” or “matrix” type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug’s release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network.

A number of relevant buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, protirelin, buserelin and oxytocin, have been delivered via the buccal route, albeit with relatively low bioavailability (0.1–5%)[54] owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa.

Buccal dosage forms can be used to treat both local and systemic conditions. A promising example of buccal mucoadhesive formulations for systemic use is the buccal delivery of salmon calcitonin (sCT) using thin-film composite containing 40 µg of sCT (200 IU) [55].

The *in vivo* studies in female New Zealand white rabbits demonstrated a relative bioavailability of 43.8±10.9%, and the reduction in plasma calcium level after the buccal administration of sCT was comparable to that observed when sCT was administered by the intravenous route. These results indicate that therapeutically effective amounts of salmon calcitonin can be delivered to the systemic circulation via the buccal mucosa. **Table 2** summarizes various buccal dosage forms described in the literature[56].

Table 2: Various buccal dosage forms

Dosage forms	Structures	Release	Effect	Active ingredients
Matrix tablets	Monolithic matrix, Coating matrix (coated on the outer side or on all but one faces), Two-layer matrix, Two-layer matrix coated with impermeable layer	Sustained or bidirectional Monodirectional Bidirectional Monodirectional	Local or systemic Systemic Local (mainly) Systemic	**Local administration**: metronidazole. **Systemic administration**: propanolol, timolol, metoclopramide, morphine sulphate, nitroglycerin, codein, insulin, calcitonin, glucagone-like peptide
Patches	Laminated film with coating layer	Monodirectional	Local or systemic	**Local administration**: diclofenac, tannic acid, boric acid. **Systemic administration**: thyrotropin-releasing hormone, octreotide, oxytocin, buserelin, calcitonin, leuenkephalin
Lipophilic gels	Cubic and lamellar liquid crystalline phases of glycerylmonooleate	–	Systemic	**Systemic administration**: (D-Ala2, D-Leu5) enkephalin
Transfersomes	Phospholipids deformable vesicles	–	Systemic	**Systemic administration**: insulin

Buccal Tablets

Tablets have been the most commonly investigated dosage form for buccal drug delivery. Buccal tablets are small, flat, and oval shaped dosage form and unlike conventional tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa and are retained in position until dissolution and/or release is complete[16]. List of investigated buccal mucoadhesive tablets is given in the following **Table 3.**

Table 3: List of investigated buccal mucoadhesive tablets

S.No.	Active ingredient	Polymers used
1	Baclofen	NaMC, Na alginate and Methocel K15M
2	Carvedilol	HPMC K4M and CP 934P
3	Carvedilol	HPMC K4M, HPMC K15M and CP 934
4	Chlorhexidine diacetate	Chitosan and Na alginate
5	Chlorpheniramine maleate	Hakea gum from *Hakea gibbosa*
6	Diltiazem	NaCMC, HPMC, Na alginate and guar gum
7	Flurbiprofen	HPMC K15M, HEC, CP971 and Carbomer 940
8	Itraconazole	Eudragit 100M, HPMC K4M and CP 934P
9	Miconazole nitrate	CP 934, HPMC K4M and PVP K30
10	Morphine sulfate	HPMC K100M, CP 910 and Eudragit RSPM
11	Nicotine	CP 934 and HPC
12	Nifedipine	CMC, CP 934P, HPMC, PVP K30 and PVA
13	Omeprazole	Na alginate, HPMC
14	Ondansetron	HPMC 15 cps, CP 934, Na alginate and NaCMC
15	Oxytocin	Mucilage of *Diospyros peregrina* fruit
16	Piroxicam	HPMC K4M and CP934
17	Pravastatin Na	PVP K-30 and Pluronic F127and EC
18	Prednisolone	HPMC, CP 934 and NaCMC
19	Propranolol HCl	Na alginate, CP 971P and PVP K30
20	Propranolol HCl	HPMC K4M, Xanthan gum, EC and acrypol 934P
21	Salbutamol sulphate	HPMC K4M and EC
22	Tizanidine HCl	CP 934, HPMC K4M, HPMC K15M and NaCMC and EC
23	Verapamil HCl	CP934 P, HPMC K4M, HEC and NaCMC

Monolithic and two-layered matrix tablets have been designed for buccal drug delivery[56]. Bioadhesive tablets may be prepared using different methods such as direct compression or wet granulation technique. For buccal drug delivery, the tablets which are inserted into the buccal pouch may dissolve or erode; therefore, they must be formulated and compressed with sufficient pressure only to give a hard tablet. To enable or to achieve unidirectional release of drug, water impermeable materials, such as ethyl cellulose, hydrogenated castor oil, etc. may be used either by compression or by spray coating to coat every face of the tablet except the one that is in contact with the buccal mucosa.

If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression in order to achieve some desirable properties, e.g. enhanced activity and prolonged drug release[57].

Buccal patches: Buccal patches are described as laminates which comprise of an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a bioadhesive surface for mucosal attachment. Two methods, namely, solvent casting method and direct milling are used to prepare adhesive patches. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate.

In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out.

Also to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period, an impermeable backing layer may be applied. The drugs and polymers that have been used to develop buccal patches are listed in **Table 4** as given below.

Table 4: List of investigated buccal mucoadhesive patches

S. No.	Active ingredient	Polymers used
1	Aceclofenac	Gelatin, Poly Na CMC and PVA
2	Atenolol	CP 934P, HPMC and NaCMC
3	Carvedilol	HPMC, CP934, Eudragit RS 100, and EC
4	Carvedilol	HPMC E15 and HPC JF
5	Cetylpyridium chloride	PVA, HEC, or chitosan
6	Hydrochlorothiazide	EC and HPMC
7	Ibuprofen	NaCMC and PVP
8	Insulin	NaCMC-DVP
9	Methotrexate	HPMC K4M, Na alginate, NaCMC, CP 934, and PVP K-30
10	Metoprolol tartrate	Eudragit NE40D with HPMC, Na CMC or CP
11	Miconazole	HPMC, NaCMC, Chitosan, HECand PVA.
12	Pentazocine	CMC, HPMC K4M, CP 974P and PVA
13	Prochlorperazine	HPMC E15
14	Propranolol HCl	Chitosan and PVP K-30
15	Salbutamol sulphate	Chitosan,PVA and PVPK30
16	Tizanidine HCl	NaCMC and CP 934
17	Triamcinolone acetonide	HPMC, Polaxamer 407 and CP971
18	Verapamil HCl	Chitosan and PVP K-30

Buccal films: In recent times, a number of mucoadhesive dosage forms for buccal drug delivery have been developed such as tablet, films, patches, discs, ointments and gels[58-67]. However, buccal films are preferable over mucoadhesive discs and tablets in terms of patient comfort and flexibility and they ensure more accurate drug dosing and longer residence time compared to gels and ointments. Buccal films also reduce pain by protecting the wound surface and hence increase the treatment effectiveness[68]. An ideal buccal film should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it should also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration[69]. The drugs and polymers that have been used to develop buccal mucoadhesive films are listed in **Table 5**.

Table 5: List of investigated buccal mucoadhesive films

S. No.	Active ingredient	Polymers used
1	Atenolol	Na alginate, CP 934P and EC
2	Carvedilol	HPMC K15,Eudragit RL100, CP-934P, NaCMC and PVP
3	Chlorhexidine diacetate	Chitosan, HPMC, Na alginate
4	Ciprofloxacin HCl	HPMC K4M, PVA
5	Famotidine	HPMC, NaCMC and PVA
6	Fentanyl	Eudragit RS, PVP K30 and PVP K90
7	Flufenamic acid	Chitosan and KollicoatIR®
8	Glibenclamide	HPC, PVP and EC
9	Glipizide	HPMC E-15, NaCMC, Eudragit RL-100 and CP 934P
10	IsosorbideDinitrate	Eudragit RL 100, CP 93P and PVP
11	IsoxsuprineHCl	HPMC, PVP K-30 and HEC
12	Ketorolac	HPMC, CP 934P, NaCMC, HPC and EC
13	Lycopene	HPMC E15, PVP K30 and CP 934
14	Metoprolol tartrate	CP934 P, Eudragit RL100, HPMC K15M and Na CMC
15	Montelukast	HPMC K4M, HPMC 50cps, Eudragit RL-100 and PVP K30
16	Ranitidine	HPMC 15 cps and PVP
17	Terbutaline sulphate	HPMC K4M, HPMCP, Chitosan, CP 934P

Buccal gels and ointments: These are semisolid dosage forms having the advantage of easy dispersion throughout the oral mucosa. The problem of poor retention of gels at the application site has been overcome by using bioadhesive formulations. Certain bioadhesive polymers for example, sodium carboxymethylcellulose[70] undergo a phase change from a liquid to a semisolid. This change enhances or improves the viscosity, resulting in sustained or controlled release of drugs. The drugs and polymers used for buccal mucoadhesive gels are listed in **Table 6**.

Table 6: List of investigated buccal mucoadhesive gels

S. No.	Active ingredient	Polymers used
1	Insulin	Pluronic F-127gel, oleic acid, eicosapentaenoic acid and docosahexaenoic acid.
2	Itraconazole	2-ethylmethyl-2 pyrrolidone, Polaxamer 188 and CP 934
3	Nystatin	Chitosan
4	Triamcinolone acetonide	Polaxamer 407 and CP 934

CURRENT ADVANCEMENT

There have been several advances in the delivery of drugs through the buccal mucosa over the last 5 years, which have resulted in a number of new buccal delivery products appearing on the market.The future potential of buccal delivery systems looks favorable. It is envisaged that in the future, buccal drug delivery will provide a platform for the successful delivery of vaccines and antigens[70]. Along with this non-invasive delivery of potent protein and peptide are also available in future.

CONCLUSION

The buccal mucosa- A novelistic route which deliver several potent drugs with increase bioavailability and reducing dose level. This potential route going interest of several scientists and for sure in coming future those routes evolve as a prime route of drug delivery of several active pharmaceutical ingredients for drug targeting and specially delivery of protein and peptide drugs.

REFERENCES

1. Aungst BJ, Rogers NJ and Shefter E. Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promoter. The J Pharmacol Exp Ther. 1988;244:23-27.
2. Aungst BJ and Rogers NJ. Site dependence of absorption-promoting actions of Laureth-9, Na salicylate, Na2EDTA, and Aprotinin on rectal, nasal, and buccal insulin delivery. Pharm Res. 1988;5:305-308.
3. Lee WE. Permeation enhancers for the nasal delivery of protein and peptide therapeutics. Bio Pharm. 1990;3:22-25.
4. Tengamnuay P and Mitra AK. Bile salt-fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength. adjuvant composition, and lipid structure on the nasal absorption of [D-Arg2] Kyotorphin. Pharm Res. 1990;7:127-133.
5. Shao Z and Mitra AK. Nasal membrane and intracellular protein and enzyme release by bile salts and bile salt-fatty acid mixed micelles: correlation with facilitated drug transport. Pharm Res. 1992;9:1992.
6. Shao Z and Mitra AK. Bile salt fatty acid mixed micelles as nasal absorption promoters. III. Effects on nasal transport and enzymatic degradation of acyclovir prodrugs. Pharm Res. 1994;11:243-250.
7. Soyani AP and Chien YW. Systemic delivery of peptides and proteins across absorptive mucosae. Crit Rev Therap Drug Carrier Systems. 1996;13:85-184.
8. Rathbone MJ and Hadgraft J. Absorption of drugs from the human oral cavity. Int J Pharm. 1991;74:9-24.
9. de Vries ME, Bodde HE, Verhoef JC and Junginger HE. Developments in buccal drug delivery. Crit Rev Ther Drug Carr Sys. 1991;8:271-303.
10. Squier CA. The permeability of oral mucosa. Crit Rev Oral Biol Med. 1991;2:13-32.
11. Bodde HE, De Vries ME and Junginger HE. Mucoadhesive polymers for the buccal delivery of peptides, structure-adhesiveness relationships. J Control Rel. 1990;13:225-231.

12. Andrews Gavin P et al. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009;71:505-518.
13. Khairnar GA and Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymer. International Journal of Pharm Tech Research. 2010;2(1):719-735.
14. Madhav NV. Satheesh et al. Orotransmucosal drug delivery systems: A review. J Control Release. 2009;140:2-11.
15. Vyas SP and Khar RK. Controlled drug delivery-concepts and advances. Vallabh Prakashan, first edition, New Delhi. 2002.
16. Bhalodia Ravi et al. Buccoadhesive drug delivery Systems: A review. International Journal of Pharma and Bio Sciences. 2010;1(2):1-32.
17. Obradovic T and Hidalgo Ismael J. Drug absorption Studies Biotechnology: Pharmaceutical Aspects. AAPS Press. 2008;7(2):167-181.
18. Junginger HE et al. Recent advances in buccal drug delivery and absorption- in vitro and in vivo studies. J Control Release. 1999;149:149-159.
19. Rossi Silvia et al. Buccal drug delivery: A challenge already won?. Drug Discov Today Technol. 2005;2(1):59-65.
20. Miller NS et al. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005;57:1666-1691.
21. Gandhi RE and Robinson JR. Bioadhesion in drug delivery. Ind J Pharm Sci. 1988;50:145-152.
22. Harris D and Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992;81:1-10.
23. Wertz PW and Squier CA. Cellular and molecular basis of barrier function in oral epithelium. Crit Rev Ther Drug Carr Sys. 1991;8:237-269.
24. Squier CA, Cox P and Wertz PW. Lipid content and water permeability of skin and oral mucosa. The J Invest Dermat. 1991;96:123-126.
25. Squier CA and Wertz PW. Structure and function of the oral mucosa and implications for drug delivery, in eds. M.J. Rathbone, Oral Mucosal Drug Delivery, Marcel Dekker, Inc., New York, New York. 1996:1-26.
26. Galey WR, Lonsdale HK and Nacht S. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J Invest Dermat. 1976;67:713-717..
27. Gandhi RB and Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv Drug Del Rev. 1994;13:43-74.
28. Squier CA and Hall BK. The permeability of mammalian non-keratinized oral epithelia to horseraddish peroxidase applied in vivo and in vitro. Arch Oral Biol. 1984;29:45-50.
29. Hill MW and Squier CA. The permeability of oral palatal mucosa maintained in organ culture. J Anat. 1979;128:169-178.
30. Tabak LA, Levine MJ, Mandel ID and Ellison SA. Role of salivary mucins in the protection of the oral cavity. J Oral Pathol. 1982;11:1-17.
31. Peppas NA and Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Control Rel. 1985;2:257-275.
32. Rathbone M, Drummond B and Tucker I. Oral cavity as a site for systemic drug delivery. Adv Drug Del Rev. 1994;13:1-22.
33. Edgar WM. Saliva: its secretion, composition and functions. Br Dent J. 1992;172:305-312.
34. Marcos Luciano Bruschi and Osvaldo de Freitas. Oral Bioadhesive Drug Delivery

Systems. Drug Development and Industrial Pharmacy. 2005;31(3): 293-310.
35. Ishida M, Nambu N and Nagai T. Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and carbopol. Chem Pharm Bull. 1982;30:980-984.
36. Collins AEM, Deasy PB, Mac Carthy DJ and Shanley DB. Evaluation of a controlled release compact containing tetracycline hydrochloride bonded to tooth for the treatment of periodontal disease. Int J Pharm. 1989;51:103-114..
37. Elkayam R, Friedman M, Stabholz, A, Soskolne AW, Sela MN and Golub L. Sustained release device containing minocycline for local treatment of periodontal disease. J Control Rel. 1988;7:231-236.
38. Samaranayake L and Ferguson M. Delivery of antifungal agents to the oral cavity. Adv Drug Del Rev. 1994;13:161-179.
39. Nagai T. Adhesive topical drug delivery system. J Control Rel. 1985;2:121-134.
40. Nagai T and Machida Y. Mucosal adhesive dosage forms. Pharm Int. 1985:196-200.
41. Aungst BJ and Rogers NJ. Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. Int J Pharm. 1989;53:227-235.
42. Siegel IA and Gordon HP. Surfactant-induced increase of permeability of rat oral mucosa to non-electolytes in vivo. Arch Oral Biol. 1985;30:43-47.
43. Shojaei AH and Li X. In vitro permeation of acyclovir through porcine buccal mucosa. Proceedings of International Symposium on Controlled Release of Bioactive Materials. 1996;23:507-508..
44. Shojaei AH and Li X. Determination of transport route of acyclovir across buccal mucosa. Proceed Int Symp. Control Rel Bioact Mater. 1997;24:427-428.
45. Manganaro AM and Wertz PW. The effects of permeabilizers on the in vitro penetration of propranolol through porcine buccal epithelium. Mil Med. 1996;161:669-672.
46. Gandhi R and Robinson J. Mechanisms of penetration enhancement for transbuccal delivery of salicylic acid. Int J Pharm. 1992;85:129-140.
47. Hoogstraate AJ, Verhoef JC, Tuk B, Pijpers A, van leengoed LAMG, Vheijden JHM, Junjinger HE and Bodde HE. Buccal delivery of fluorescein isothiocyanate-dextran 4400 and the peptide drug buserelin with glycodeoxycholate as an absorption enhancer in pig. J Control Rel. 1996;41:77-84.
48. Wolany GJM, Munzer J, Rummelt A and Merkle HP. Buccal absorption of Sandostatin (octreotide) in conscious beagle dogs. Proceed. Intern Symp. Control Rel Bioact Mater. 1990;17:224-225.
49. Nakane S, Kakumoto M, Yulimatsu K and Chien YW. Oramucosal delivery of LHRH: Pharmacokinetic studies of controlled and enhanced transmucosal permeation. Pharm Dev Tech. 1996;1:251-259.
50. Steward A, Bayley DL and Howes C. The effect of enhancers on the buccal absorption of hybrid (BDBB) alpha-interferom. Int J Pharm. 1994;104:145-149.
51. Senel S, Hoogstraate AJ, Spies F, Verhoef JC, Bos-van Geest A, Junginger HE and Bodde HE. Enhancement of in vitro permeability of porcine buccal mucosa by bile salts: kinetic and histological studies. J Control Rel. 1994;32:45-56.
52. Hoogstraate AJ, Senel S, Cullander C, Verhoef J, Junginger HE and Bodde HE. Effects of bile salts on transport rates and routes of FTIC-labelled compounds across porcine buccal epithelium in

vitro. J Control Rel. 1996;40:211-221.
53. Wani Manish S. Current status in buccal drug delivery system. Pharmainfo.net. 2007;5(2).
54. Veuillez F et al. Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm. 2001;51:93-109.
55. Cui Z and Mumper RJ. Buccal transmucosal delivery of calcitonin in rabbits using thin-film composites. Pharm Res. 2002;19:1901-1906.
56. Rossi Silvia et al. Buccal drug delivery: A challenge already won. Drug Discov Today Technol. 2005;2(1):59-65.
57. Giunchedi et al. Formulation and in vivo evaluation of Chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. Eur J Pharm Biopharm. 2002;53:233-239.
58. Khairnaret al. Development of mucoadhesive buccal patch containing Aceclofenac: In Vitro evaluations. International Journal of PharmTech Research. 2009;1(4):978-981.
59. Adhikariet al. Formulation and evaluation of buccal patches for delivery of Atenolol. AAPS PharmSciTech. June 2010.
60. Boyapally H et al. Controlled release from directly compressible Theophylline buccal tablets. Colloids Surf B Biointerfaces. 2010;77:227-233.
61. Ikinci G et al. Development of a buccal bioadhesive Nicotine tablet formulation for smoking cessation. Int J Pharm. 2004;277:173– 178.
62. Yehia SA et al. Fluconazole mucoadhesive buccal films: In Vitro/In Vivo performance. Current Drug Delivery. 2009;6:17-27.
63. Rasool BKA and Khan SA. In Vitro evaluation of Miconazole buccal films. International Journal of Applied Pharmaceutics. 2010;2(4): 23-26.
64. Ali J, Khar R et al. Buccoadhesive erodible disk for treatment of oro-dental infections: design and characterization. Int J Pharm. 2002;283:93–103.
65. El-Samaligy MS et al. Formulation and evaluation of Diclofenac sodium buccoadhesive discs. Int J Pharm. 2004;286:27– 39.
66. Morishita M et al. Pluronic® F-127 gels incorporating highly purified unsaturated fatty acids for buccal delivery of Insulin. Int J Pharm. 2001;212: 289-293.
67. Shin et al. Enhanced bioavailability by buccal administration of Triamcinolone acetonide from the bioadhesive gels in rabbits. Int J Pharm. 2000;209:37– 43.
68. Arakawa Y et al. Effect of low-molecular-weight β-cyclodextrin polymer on release of drugs from mucoadhesive buccal film dosage form. Biol Pharm Bull. 2005;28:1679-1683.
69. Patel VM et al. Effect of hydrophilic polymers on buccoadhesive Eudragit patches of Propranolol Hydrochloride using factorial design. AAPS PharmSciTech. 2007;8(2):1-8.
70. Wong et al. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm. 1999;178:11-22.