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REVIEW ARTICLE

Buccal Mucosa as a route for Drug Delivery: Mechanism, Design and Evaluation

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ABSTRACT

Since the early 1980s there has been renewed interest in the use of bioadhesive polymers to prolong contact time in the various mucosal routes of drug administration. As we all know that, the buccal cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism. The release of drug from the buccal mucosa is continuously affected by mucus secreted from salivary gland. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutics agents such as peptides, oligonucleotides and polysaccharides. Absorption enhancer may be required to overcome this delivery. And by changing mucus rheology, increasing the fluidity of lipid bilayer membrane, acting on the components at tight junctions, by overcoming the enzymatic barrier, increasing the thermodynamic activity of drugs. And along with those different types of diffusions, intercellular movements and endocytosis, this process take part to delivers of the novel drugs by buccal mucosa as systemic delivery. The main aim our review is to focus on the mechanism for the delivery of drug as a novel carrier by matrix, reservoir, and patch, design to systemic delivery, and without the changing of pattern of evaluation for buccal systemic delivery, can be used as a potential drug delivery. And in the fields of novel drug delivery systems the most acceptable and challenging role is accomplishing by one of the most acceptable and challenging route buccal mucosa as systemic drug delivery.

Keywords: buccal mucosa, bioadhesive, sustain.

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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 disadvantage such as hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits 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 lining of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantage 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.

The nasal cavity as a site for systemic drug delivery has been investigated by many research groups [1-7] and the route has already reached commercial status with several drugs include LHRH [8-9] and calcitonin. However , the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms, as well as the large intra- and inter- subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal, and ocular mucosal all offer certain advantages, 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 [14-15] and the virtual lack of langerhans cells [16] makes the oral mucosa tolerant to potential allergens, furthermore, oral Transmucosal drug delivery bypass first pass effect and avoids presystemic 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:

(1) **Sublingual delivery**: consisting of administration through the membrane of the ventral surface of the tongue and the floor of the mouth. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted [8].

(2) **Buccal delivery**: consisting of administration through the buccal mucosa, mainly composed of the lining of the cheeks. 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.

(3) **Local delivery**: consisting of administration through all areas other the former two regions. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches [9] periodontal diseases [10,11] bacterial and fungal infections

[12] and aphthous and dental stomaitis [13] and in facilitating tooth movement with prostaglandins [14] However , the preferred site for retentive oral Transmucosal delivery systems and for sustained- and controlled- release delivery devices is the buccal mucosa [8-15].

These sites differ anatomically in their permeability to drugs, rate of drug delivery, and ability to maintain a delivery system for the time required for drug release out of the delivery apparatus and into the mucosa.

Advantage of drug delivery via the buccal lining:

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism.
2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients.
3. Sustained drug delivery.
4. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
5. Increased ease of drug administration.

Limitations of buccal drug delivery

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows,

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
2. The non-uniform distribution of drug within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

1. ORAL MUCOSA

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (figure 1). Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer [15]. The epithelium of the buccal mucosa is about 40-50 cell layers thick. The turnover time for the buccal epithelium has been estimated at 5-6 days. The oral mucosal thickness varies depending on the site; the buccal mucosa measures at 500-800µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral

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tongued, and the gingivae measure at about 100-200µm. the mucosae of the soft palate, the sublingual, and the buccal regions, are not keratinized [27] .The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function.

The non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides [28]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia In the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor glands [26-28]. At physiological pH the mucus network carries a negative charge (due to 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 [17].

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 [26-28]. The salivary pH range from 5.5 to 7 depending on the flow rate.

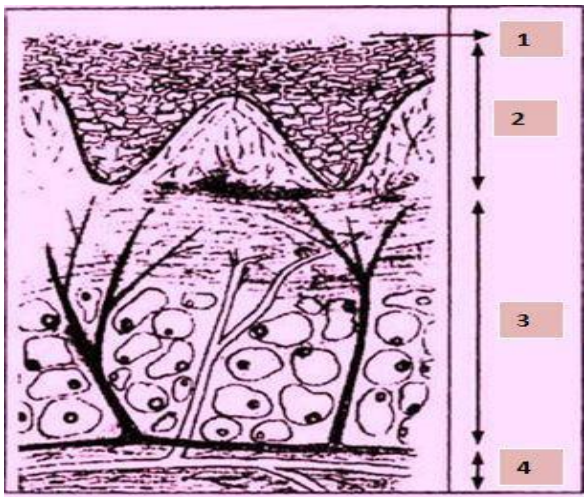

Figure 1: Structure of the mucosa of the oral cavity: 1) mucus layer; 2) epithelium; 3) connective tissue (lamina propria); 4) smooth muscle layer (kharenko et al., 2009

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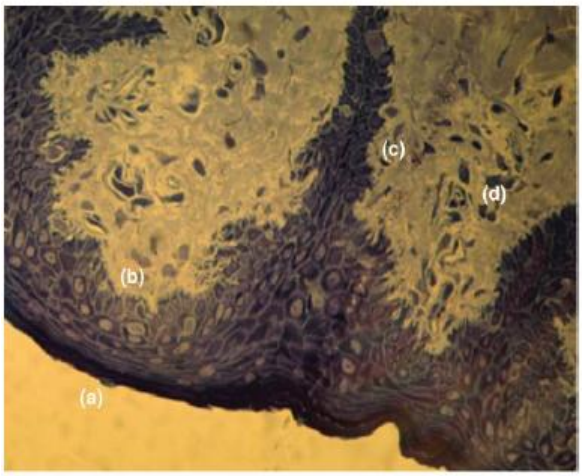

Figure 2: Section of the buccal epithelium. (a) Superficial layer; (b) basal layer; (c) basal membrane and (d) lamina propria (underlying the connective tissue).

2. 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. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. 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. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. 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. Up to 70% of the total mucin found in saliva is contributed by the minor salivary gland. 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. 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. 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.

Role of saliva

- 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

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

3. Permeability

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intracellular lipids produced by membrane- coating granules. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin [3]. The permeability's of the oral mucosa decreases in the order of sublingual greater than buccal and buccal greater than palatal [4]. This is based on the relative thickness and degree of keratinization of these tissues. The permeability barrier in the oral mucosa is a result of intercellular material obtained from "membrane coating granules" (MCG). This barrier exists in the outermost 200µm of the superficial layer.

Passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other mucosa (that of the tongue) for a few drugs and nutrients: glucose and cefadroxil were shown to be absorbed in this way.

The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutics agents such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancer may be required to overcome this delivery.
The buccal mucosa also contains proteases that may degrade peptide- based drugs. In addition, the salivary enzymes may also reduce stability.

Disease state where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions.

4. Permeation Enhancers

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as permeation enhancers (Chatta-rajee et al., 1995). As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action.

However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific (Shobjaei 1998). Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal mucosa. These permeation enhancers should be safe and non toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic (Aungst 1994). However, examination of penetration route for transbuccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability.

Mechanism of action of permeation enhancers [8]

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows. (Ganem et. al., 1996). Also summarized in Table (2)

1) Changing mucus rheology

Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

2) Increasing the fluidity of lipid bilayer membrane

The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.

3) Acting on the components at tight junctions

Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

4) By overcoming the enzymatic barrier

These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

5) Increasing the thermodynamic activity of drugs

Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to increased thermodynamic activity resulting better absorption.

Mechanism of drug absorption by buccal route

1. **Simple diffusion:** absorption path is based on random motion of molecules from a zone of higher concentration to one of low concentration to substance placed on mucosa.

2. **Facilitated diffusion:** absorption involves a carrier system which leads to more rapid absorption such a carrier system exhibit stereo specificity in D- glucose and L-arabinose. Absorption of nicotinic acid and nicotinamide across the buccal mucosa has been shown to depend upon the presence of sodium ions.

3. **Intercellular movements:** oral epithelium has loose junctions and is leaky therefore is likely to allow passage of substance through intercellular space. The basal lamina limits the passage of molecules with a molecular weight more than 70,000.

4. **Endocytosis:** although cells of oral mucosa are able to absorb substances by endocytosis it is likely that this mechanism has only a minor role in drug transport from oral cavity.

Factor affecting drug delivery via buccal route

(a) Nature of permeant

Most drug move extracellularly through the neutral lipids and glycolipids that separate the mucosal cells. There the lipid solubility of drugs is an important in TMDD suitability.

Along with lipid solubility, drugs selected for TMDD must have physiochemical properties, including size and pka that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentration.

(b) Molecular size

For hydrophilic macromolecules such as peptides, absorption enhancers(see later section) have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules [26].

(c) Lipid solubility and partition coefficient

Only the nonionized forms of molecules have the ability to cross lipoidal membranes in significant amounts. The more lipids soluble a compound is, the higher its permeability. The

permeabilities for these compounds are direct functions of their oil-water partition coefficient. The partition coefficient is a useful tool to determine the absorption potential of a drug. In general, increasing a drug's polarity by ionization or the addition of hydroxyl, carboxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient. Conversely decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility. the partition coefficient is also an important indicator of drug storage in fat deposits. Obese individuals can store large amounts of lipid-soluble drug in fat stores. These drugs are dissolved in the lipid and are a reservoir of slow release from these fat deposits.

(d) Ionization

The ionization of a drug is directly related to both its pka and ph at the mucosal surface . Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases

Methods to increase drug delivery via buccal route

Absorption enhancers

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inters/ intracellular lipids, altering cellular proteins or altering surface mucin. The most common enhancers are azone, fatty acids, bile salts, and surfactants such as sodium dodecyl sulfate. Solution/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism [1].

Table 1: List of permeation enhancers

Sl. No	Permeation enhancers	Sl. No	Permeation enhancers
1	2,3- lauryl ether	14	Phophatidylcholine
2	Aprotinin	15	Polyoxyethylene
3	Azone	16	Polysorbate 80
4	Benzalkonium chloride	17	Polyoxyethylene
5	Cetylpyridinium chloride	18	Phophatidylcholine
6	Cetyltrimethyl ammonium bromide	19	Sodium EDTA
7	Cyclodextrin	20	Sodium glycocholate
8	Dextran sulfate	21	Sodium glycodeoxycholate
9	Glycol	22	Sodium lauryl sulfate
10	Lauric acid	23	Sodium salicylate

11	Lauric acid/ propylene	24	Sodium taurocholate
12	Lysophosphatidylcholine	25	Sodium taurodeoxycholate
13	Menthol	26	sulfoxides

Structure & Design of Buccal dosage form

Structure and design

Drug delivery designed for the buccal mucosa contains a polymeric adhesive component. When in contact with the saliva, the adhesive attaches to the mucosa causing immediate and rapid drug delivery. Transmucosal drug delivery systems can be unidirectional or bi-directional. Unidirectional patches release the drug only into the mucosa, while bi-directional patches release the drug in both the mucosa and the mouth. The buccal patch is designed in either a matrix configuration with drug, adhesive, and additives mixed together, or a reservoir system that contains a cavity for the drug and additives separate from the additives.

An impermeable backing is applied to control the direction of drug delivery, to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Buccal dosage form for buccal delivery

In the past decades, to till now, different drug delivery systems intended for buccal administration have been developed. The most common buccal dosage forms are tablets and patches. Such type of form must be of a small size and a suitable geometry so as to not interfere with physiological function of the mouth, even after their hydration in the oral cavity. One of the requirements is that they do not adhere too tightly because it is undesirable to exert too much force to remove the formulation/ dosage form after use, otherwise the mucosa could be injured. An alternative is the use of formulations that dissolve or disintegrate completely during the application period. Moreover, in the case of Transmucosal administration, Drug release should be unidirectional (towards the mucosa), and the release into the saliva should be avoided.

Matrix type

The buccal patch designed in a matrix configuration contains drug, adhesive, and additive mixed together. Monolithic and two –layered matrix type have been designed for buccal delivery of drugs. In fig. 3, a schematic representation of several kinds of matrix tablets in given. Monolithic tablets consist of a mixture of drug with a swelling bioadhesive/ sustained release polymer (fig. 3a) with a bidirectional release .They can be coated on the outer or on all sides but one face with water.

Impermeable hydrophobic substances to allow a unidirectional drug release for systemic delivery (Fig. 3b and c). Two layered tablets comprise an inner layer based on a bioadhesive polymer and an outer non-bioadhesive layer containing the drug for a bi-directional release but mainly a local action (Fig. 3d). In the case of systemic action, the drug is loaded into the inner bioadhesive layer whereas the outer layer is inert and acts as a protective layer (Fig. 3e). Alternatively, the drug is loaded into a controlled release layer and diffuses towards the absorbing mucosa through the bioadhesive layer, whereas a water impermeable layer assures the monodirectional release (Fig. 3f). Different drugs have been loaded in matrix tablets, such as propanolol, timolol, metronidazole, metoclopramide, morphine sulphate, nitroglycerin and codein . Peptides, such as insulin, calcitonin and glucagone-like peptide were also loaded in buccal mucoadhesive tablets.

Reservoir types

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Patches

Patches are laminated and generally consist of an impermeable backing layer and a drug-containing layer that has mucoadhesive properties and from which the drug is released in a controlled manner. Moreover, buccal patches for systemic delivery of tyrotropin-releasing hormone, octreotide, oxytocin, buserelin, calcitonin and leuenkephalinhave been studied.

Novel drug delivery system

Novel drug delivery systems, such as lipophilic gel, buccal spray and phospholipids vesicles have been recently proposed to deliver peptides via the buccal route. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been already developed. This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium, and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a number of advantages including rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit) and bolus delivery of drug.

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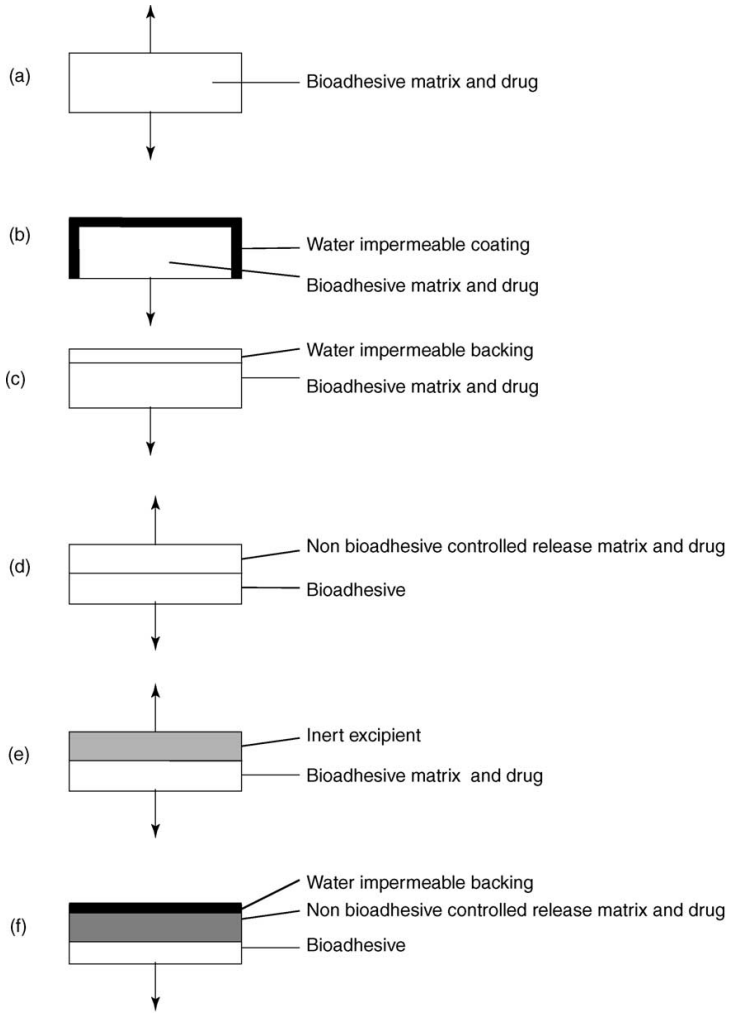

Figure 3. Schematic representation of different matrix tablets for buccal delivery. Arrows indicate the direction of drug release.

METHODOLOGY FOR BUCCAL PERMEABILIY STUDIES

- **In vitro method**

To date, we have no standard means by which the viability or the integrity of the dissected tissue can be assessed. Dowty et al. studied tissue viability by using ATP levels in rabbit buccal mucosa [16]. They reported a 50% drop in the tissue ATP concentration during the initial six hours of the experiment without a corresponding drop in tissue permeability.

Buccal cell culture also has been suggested as useful in vitro models for buccal drug permeation and metabolism [17-20]. To use these cell cultures for buccal drug transport experiments, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled. In a series of systematic studies, Jacobsen et

al. and Nielsen et al. reported on the use of a human buccal cell lines, TR 146, grown on filters as a model for buccal permeation experiments [21-25]. This model cell culture has been well characterized in terms of morphology, barrier properties, and cell differentiation and shown to be a promising screening tool to study passive transport of various model compounds across buccal .epithelium.

- **In vivo method**

In vivo method were first originated by beckett and trigs with the so called buccal absorption test [26]. Using this method, they measured the kinetics of drug absorption. The methodology involves the swirling of a 25-ml sample of the test solution for as long as 15 min in the mouth by human volunteers, followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined to assess the amount of drug absorbed. Various modification of the buccal absorption test has been tested, corrected for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization [27-30]. A feasible approach to achieve absorption site localization is to retain the drug on the buccal mucous using a bioadhesive system. Other in vivo methods include those carried out via a small perfusion chamber to the upper lip of anesthetized dogs. The perfusion chamber is attached to the tissue by cyano-acrylate cement. The drug solution is circulated through the device for a predetermined period of time. Sample fractions then are collected from the perfusion chamber to determine the amount of drug remaining in the chamber, and blood samples are drawn after 0 and 30 min to determine the amount of drug absorbed across the mucosa.

- **Experimental animal species**

Aside from the specific methodology used to study buccal drug absorption and permeation characteristic, special attention is warranted to the choice of experimental animal species for such experiments. For in vivo investigations, many researchers have used small animals including rats [1] and hamsters for permeability studies. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue and has been extensively utilized in experimental studies. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys Dog And pigs.

- **Toxicity and irritancy associated with buccal drug delivery [29]**

Carbomers have been reported to produce mucosal irritation believed to result from a localized low ph, whereas lectins have been shown to be cytotoxic. Excipients such as absorption enhancers (e.g., sodium dodecyl sulfate) have also been reported to be irritant.

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List of Active in gradients delivered via buccal route

1.	Acitretin	26	Melatonin
2.	Acyclovir	27	Metoprolol tartarate
3.	Arecoline	28	Morphine sulphate
4.	Buprenorpine	29	Nalbuphine
5.	Carbamazepine	30	Nicotine
6	Cetyl pyridimium chloride	31	Nifedipine
7	Chlorhexidine diacetate	32	Omeprazole
8	Chitosan	33	Oxytocin
9	Chlorpheniramine maleate	34	Pentazocine
10	Cyanocobalamin	35	Protirelin
11	Danazol	36	Pindolol
12	Denbufylline	37	Piroxicam
13	Diclofenac sodium	38	Propranolol
14	Dilitiazem hydrochloride	39	Propolis
15	Ergotamine tartarate	40	Recombinant human epidermal growth factor (Rh EFG)
16	Fluride	41	Salmon calcitonin
17	Flurbiprofen	42	Sodium fluoride
18	Glucagon- like peptide (GLP)-1	43	Testosterone
19	Hydrocortisone acetate	44	Terbutaline sulphate
20	Insulin	45	Theophyline
21	Lactoferrin	46	Thyotrophin releasing hormone
22	Lignocaine	47	Triamcinolone acetate
23	Leu-enkephalin	48	Zinc sulphate.
24	Leutinizing hormone releasing hormone (LHRH)	49	
25	Metronidazole	50	

Summary and conclusion

The buccal mucosa offers several advantages for controlled drug delivery for extended period 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. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. 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 safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. Buccal delivery of drugs provides an attractive alternate to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal

cavity. It is also possible to administer drugs to patients who cannot be dosed orally. Therefore, adhesive mucosal dosage forms were suggested for oral delivery that included adhesive tablets adhesive gels and adhesive patches. However, buccal films are preferable over adhesive tablets in terms of flexibility and comfort.

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