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Journal of Pharma Research

Journal of Pharma Research
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www.jprinfo.com

Review Article
ISSN: 2319-5622

Buccal Drug Delivery system- Approach to Improve the Bioavailability

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Received on: 20-05-2015; Revised and Accepted on: 03-06-2015

ABSTRACT

Buccal delivery of drugs provides an attractive alternate to the oral route of drug administration, particularly in disadvantages associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering drug via buccal route. Moreover the oral cavity is easily accessible for self medication and can be promptly in case of toxicity just by removing the dosage form from buccal cavity. It is also possible to administer drug for those who cannot be dosed orally via this route.

Keywords: *Buccal drug delivery, Bioadhesion, Permeability enhancer, Oral mucosa.*

INTRODUCTION

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. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability· Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism [1]. Amongst the various routes of drug delivery, oral route is the most preferred to the patient. However, disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract limits its use for certain drugs. Different absorptive mucosa is considered as potential site for drug administration. Example- nasal, rectal, vaginal, ocular and oral cavity Non-invasive systemic administration. Local targeting / systemic drug delivery. This drug delivery system utilizes property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting particular site. Buccal delivery is the administration of the drug via buccal mucosa (lining of the cheek) to the systemic circulation.

There are four potential areas for drug delivery in the oral cavity, namely

- Buccal
- Sublingual
- Palatal
- Gingival

Buccal drug delivery specifically refers to the delivery of drugs within/through the buccal mucosa to affect local/systemic pharmacological actions. [2, 3]

Need for Study:

Local drug delivery to mouth includes any system that is applied to the oral mucosal membrane to treat conditions of the mouth such as periodontal disease, gingivitis, oral candidasis and other chronic lesions or topical bacterial fungal infections.

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Traditional methods of delivery to the diseased site include chewing gums, mouthwashes and ointments. However, these suffer common disadvantages in that they all have relatively short residence time and therefore, fail to maintain therapeutic concentrations for long duration to affect the bacterial population. Moreover, drug is lost in the saliva (by swallowing), and patients on these treatments often have low patient compliance due to the need for frequent drug application. However, current research attempts are made to prolong residence time and increase patient compliance by using sustained release drug delivery systems such as tablets, film and gel, which are bioadhesive in nature. The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in the gastrointestinal tract and first passes metabolism. There are four potential regions for drug delivery in the oral cavity, namely buccal, sublingual, palatal and gingival. Buccal drug delivery specifically refers to the delivery of drugs within/ through the buccal mucosa to affect local/ systemic pharmacological actions. Buccal delivery drugs may be used for treatment of diseases in the oral cavity or for systemic use and also to bypass the first pass metabolism effect [4].

Anatomy and Nature of Oral Mucosa: [4]

Oral mucosa is lined with an epithelium supported by a connective tissue termed lamina propria and separated from the epithelium by basal membrane. Epithelium of oral mucosa is stratified with regional variation in terms of structure and function. Three types of oral mucosa are referred to as.

- Masticatory
- Lining
- Specialized mucosa

The epithelium of masticatory mucosa in gingival and hard palate regions is keratinized and further subdivided into four layers, namely,

- Keratinized
- Granular
- Prickle-cell and,
- Basal layers.

The non-keratinized epithelium of lining mucosa covers the remaining regions, except the dorsal surface of the tongue and is made up of superficial, intermediate, prickle-cell and basal layers. Specialized mucosa in the dorsum of the tongue consists of both keratinized and non-keratinized mucosa. The physiological structure of oral cavity is illustrated in Fig. 1 & 2.

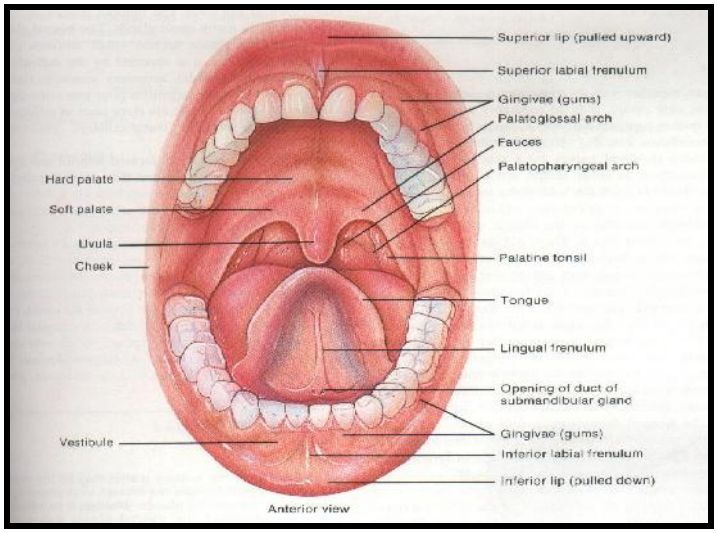

Fig. 1: Oral cavity

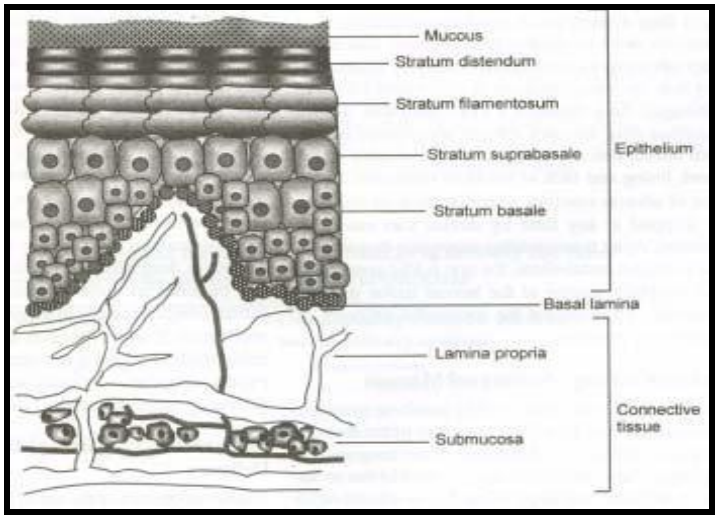

Fig. 2: Schematic diagram of cross section of oral mucosa.

Blood Supply:

Small vessels and capillaries that open to internal jugular vein distribute within the lamina propria thus avoiding the hepatic first pass clearance of buccal delivered drugs. Blood flow in the oral mucosa is faster and richer than that in the skin. The non-keratinized buccal mucosa thickness is 500-600 µm, which has surface area of 50.2 cm^2.

Table No. 1: Oral Epithelium characteristics

Tissue	Structure	Epithelial thickness (µm)	Blood flow
Buccal	Non-Keratinized	500-600	2-40
Sublingual	Non- Keratinized	100-200	0.97
Gingival	Keratinized	200	1.47
Palatal	Keratinized	250	0.89

The keratinized epithelium contains more neutral lipids that are associated with the barrier function, while non-keratinized epithelia certain more polar lipids. The loosely packed intercellular lipids and the presence of large amounts of phospholipids in non keratinized, even in keratinized mucosa account for the overall higher permeability of the oral mucosa than that of the skin stratum corneum. The non-keratinized mucosa is permeable than the keratinized mucosa.

Secretion of Saliva: [5]

The secretion of saliva from salivary glands features regional, individual, and time variations. The buccal region contains minor salivary glands. The surface of the buccal mucosal membrane is constantly washed by a stream of about 0.5 to 2 liters of saliva daily produced by the salivary glands, however exact calculation have shown that the total production of saliva is 500-600ml/day.

Mucus Layer:

The tissue layer responsible for formation of the adhesive interface is mucus. Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans. It is secreted by the goblet cells lining epithelia or by special exocrine glands with mucus cells acini. The lubrication properties of mucus secretions are result of this viscous and gel forming properties and general stickiness.

It has the following general composition

Water	:	95 %
Glycoproteins and lipids	:	0.5-5 %
Mineral salts	:	1 %
Free proteins	:	0.5-1 %

Physiological Aspects of Buccal Mucosa: The buccal mucosa has a very limited area for application of the buccal delivery system, thus it depends upon the size of dosage form. Generally, a device with size of 1-3cm^2 and a daily dose of 25 mg or less would be preferred for buccal delivery. The maximal duration of buccal drug delivery is approximately 6-8 hr.

Pharmacokinetics of Buccal Mucosa:

1. Absorption: The vascularity of the oral cavity, combined with a thin epithelial lining, allows for absorption of drugs at a rapid rate.

Non-ionized drugs take advantage of these tissue characteristics and diffuse rapidly. The drugs used to restrain plaque levels are highly ionized and therefore, are generally unable to penetrate the oral mucosa.

2. Distribution: Once an agent is applied in the oral cavity, free drug can act at the primary site (i.e. bacteria in the plague) or it can partition to compartments where drugs bind non- specifically. The agents bind non-specifically and reversibly to oral reservoirs, which is an important quality for sustained release of drugs.

3. Metabolism: In the oral cavity, drug metabolism occurs in mucosal epithelial cells.

4. Excretion: Salivary flow is important in the removal of many agents from the oral cavity.

5. Substantivity: The period that a drug is in contact with particular substrate in the oral cavity is defined as substantivity. Drugs that have prolonged duration of contact are considered to have high substantivity. Oral cavity substantivity depends upon two pharmacokinetic features

a) Degree of reversible, non-specific binding to oral reservoirs.
b) Rate of clearance by salivary flow

The oral compartments that accumulate drug must be able to reversibly bind large portions of the administered dose and release therapeutic concentration of free drug to the site of action over long periods of time.

Salivary flow: The clearance of an agent from oral cavity is directly proportional to the rate of salivary flow. High flow results in greater release of drugs. So, strategies that utilize natural or drug induced periods of low salivary flow can increase the substantively of an oral agent**.**

Bioadhesion: [2]

For bioadhesion to occur, a succession of phenomena is required, i.e Initial contact between the two surfaces and formation of secondary bonds due to non-covalent interactions. Bioadhesive is the term that describes the adhesion of a polymer to a biological substrate. More specifically, when adhesion is restricted to the mucous layer it is termed as mucoadhesion. Considerable interest is seen in the concept of bioadhesion. The immobilization of drug carrying particles at the mucosal surfaces would result in, prolonged residence time at the site of action or absorption and localization of the drug delivery system at a given target site.

Theories of Bioadhesion:

Several theories have been proposed to explain the fundamental mechanisms of adhesion.

1. Electronic theory: According to this theory, electron transfer occurs upon the contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structure. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

2. Absorption theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces.

Two types of chemicals bonds are
1) Primary chemical bonds of covalent nature.
2) Secondary chemical bonds including electrostatic forces, Vander Waals forces and hydrogen and hydrophobic bonds.

3. Wetting theory: Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant. The work of adhesion [expressed in terms of surface and interfacial tension (Y) being defined as energy per cm^2 released when an interface is formed.

According to Dupres equation work of adhesion is given by

$$Wa = YA + YB - YAB$$

Where A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$Wc = 2YA \text{ or } YB$$

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$SB/A = YA - (YB+YAB)$$

SB/A should be positive for a bioadhesive material to adhere to a biological membrane.

4. Diffusion theory: According to this theory, the polymer chain and the mucus mix to sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucous depends on the diffusion co-efficient and the time of contact. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to be considered.

Drug Characteristics Necessary for the Oral Mucosal Drug Delivery System Design: [4]

Following are the characteristics which makes the drug an ideal candidate to be formulated into buccal drug delivery system.

I. Physicochemical Characteristics:

1. Molecular Size and Weight:

Molecular size and weight influence the diffusivity of the drug through the epithelial layer. As a general rule, the larger the molecule, the more difficult it is to move about, and the lower will be the diffusivity. For large molecules in non-homogeneous tissues (such as the epithelium), the dependence of diffusivity on molecular weight would be evident because of physical hindrance of movement as the molecular size of the drug approaches the dimensions of the pathways available for diffusion. For hydrophilic drugs, small molecules appear to cross oral mucosa rapidly, however, permeability falls off rapidly as molecular size increases and has been observed to decrease sharply as molar volume is increased beyond 80 ml/mol. For lipophilic drugs the relationship between size and permeability has not been demonstrated across oral mucosa, however, investigators have suggested that such a relationship is likely to exist.

2. Degree of lonization:

The average pH of saliva is 6.6. Because the un-ionized form of a drug is the lipid soluble-diffusible form, the pKa of the drug plays an important role in its absorption across the lipid membranes of the oral mucosa.

3. Lipid solubility:

For a series of unionized compounds, those with greater lipid solubility, exhibit higher permeability across oral mucosa.

II. Biopharmaceutical Characteristics:

1. Organoleptic Properties:

The organoleptic properties of a drug or the delivery system may result in poor patient compliance or acceptance of the product. The detection of bad taste when the drug or delivery system excipients reach the taste buds would be detrimental to the success of the delivery system. The texture of the delivery system may also affect patient compliance or acceptability.

2. Daily Dose Size:

The total amount of drug that could be systemically delivered across buccal mucosa from a 2 cm^2 system in one day has been estimated to be 10-20 mg. Therefore, buccal drug delivery is suitable only for drugs whose daily dose is in the order of a few mg.

3. Drug biological half-life:

Drugs with short biological half-lives may be considered potentially useful candidates for buccal delivery.

4. Toxicity to oral mucosa:

The irritancy/sensitization debate should not only be limited to the drug but also to the components of the delivery system which are also in intimate contact with the oral mucosa.

Ideal Drug Candidates for Buccal Drug Delivery System:

1. Molecular weight between 200-500 daltons.
2. Drug should be lipophilic or hydrophilic in nature.
3. Stable at buccal pH.
4. Taste – bland
5. Drug should be odourless.
6. Drugs which are absorbed only by passive diffusion should be used.

Drug Permeability through Buccal Mucosa:

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

- Intracellular (Transcellular, passing through the cell) and;
- Extracellular (Paracellular / intercellular passing around the cell).

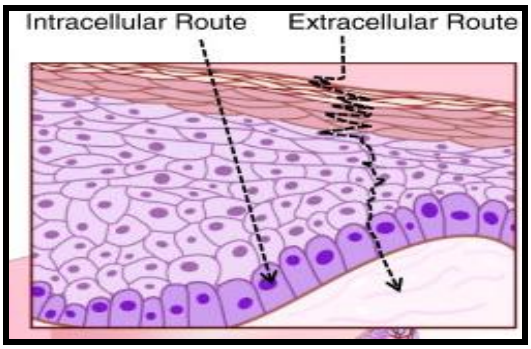

Fig. 3: The intracellular and extracellular routes of transport have been designated to the buccal mucosa.

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 squat partition coefficient. Therefore, the intercellular spaces pose as the main 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. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

Permeability Enhancers:

Permeability enhancers are substances added to pharmaceutical formulation in order to increase the membrane permeation rate or absorption rate of coadministered drug.**E.g. :** By using di- and tri-hydroxy bile salts, the permeability of buccal mucosa to fluorescein isothiocynate (FITC) increased by 100-200 fold compared to FITC alone.

Applications - Enhance bioavailability of drugs – 5% – 40%
Limitations - May cause potential membrane damage.

Table No. 2: Different Permeation Enhancers used in Buccal drug delivery

Class of permeation enhancers	Examples
Thiolated polymers	Chitosan-4-thiobutylamide, chitosan-4-thiobutylamide / GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarbophil-cysteine, polycarbophil-cysteine / GSH, chitosan-4-thioethylamide / GSH , chitosan-4-thioglycholic acid
Surfactants	Sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-lauryl ether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide
Chelators	EDTA, citric acid, sodium salicylate, methoxy salicylates.
Non-surfactants	Unsaturated cyclic ureas.
Fatty acids .	Oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine
Inclusion complexes	Cyclodextrins.
Bile salts .	Sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate
Others	Aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides.

Mucoadhesive Dosage forms satisfy several features of Controlled Release Systems:

- Localize the drug, in particular regions, thereby improving and enhancing the bioavailability of drug.
- The strong interaction between the polymers and the mucosal lining of the tissues helps in increasing contact time and permit localization.
- Inhibit metabolizing enzymes in a localized area.
- Deliver agents locally for the purpose of modulating antigenicity.

Advantages of Mucoadhesive Buccal Drug Delivery: [6-9]

Drug administration via the oral mucosa offers several advantages:

- Ease of administration and termination of therapy in emergency.
- Permits localization of the drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious and trauma patients.
- Offers an excellent route for the systemic delivery of drug which bypasses first pass metabolism, thereby offering a greater bioavailability.
- Significant reduction in dose can be achieved, thereby reducing dose, dose dependent side effects, and eliminates peak-valley profile.
- Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered by this route.

- It offers a passive system for drug absorption and does not require any activation.
- It can be made unidirectional to ensure only buccal absorption.
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
- Flexibility in physical state, shape, size and surface.
- Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.
- It satisfies several features of the controlled release system.
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than skin.
- The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus buildup beneath the applied dosage form.
- Rapid onset of action.

Limitation of Buccal Drug Administration: [6-9]

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Only drug with small dose requirement can be administered.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Eating and drinking may become restricted.
- There is an ever present possibility of the patient swallowing the dosage form.
- Over hydration may leads to slippery surface and structural integrity of the formulation may get disrupted by this. Swelling and hydration of the bioadhesive polymers may occur.
- Drugs contained in the swallowed saliva follows the peroral route and the advantages of buccal route are lost.

Design of Buccal Dosage form: [10]

1. Matrix Type:

The Buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth. The structure of the matrix type design is basically a mixture of the drug with the mucoadhesive matrix.

2. Reserviour Type:

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. 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.

Buccal Mucoadhesive Dosage forms:

Three types based on their geometry

1. single layer device with multidirectional release significant drug loss due to swallowing
2. impermeable backing layer is superimposed preventing drug loss into the oral cavity
3. unidirectional release device, drug loss is minimal achieved by coating every face except contact face

I. Buccal Formulations:

1. Buccal Tablets:

Most commonly investigated dosage form for Buccal drug. Tablets are small, flat, and oval, with a diameter of approximately 5–8 mm. Tablets can be applied to different sites in the oral cavity. The main drawback is lack of physical flexibility, poor patient compliance.

2. Buccal Patches:

Laminates consisting of an impermeable backing layer, a drug-containing reservoir layer, a bioadhesive surface for mucosal attachment. Similar to those used in transdermal drug delivery. Backing layer control the direction of drug release, prevent drug loss, minimize deformation and disintegration.

3. Buccal Films:

Most recently developed dosage form for Buccal administration. Preferred over adhesive tablets in terms of flexibility and comfort. Flexible, elastic, and soft, yet adequately strong. Effective in oral disease.

4. Buccal Gels:

Semisolid dosage forms, have the advantage of easy dispersion throughout the oral mucosa. May not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations.

Table No. 3: Mucoadhesive Polymers used in the Oral Cavity

Criteria	Categories	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Synthetic	**Cellulose derivatives:** [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC,MC, Methyl hydroxyl ethyl cellulose] **Poly(acrylic acid)-based polymers:** [CP, PC, PAA, polyacrylates, poly (methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly (acrylic acidco ethylhexylacrylate), poly (methacrylate), Poly (alkylcyanoacrylate), poly (isohexylcyanoacrylate),Poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG] **Others:** Polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, Sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate,sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly (methacrylic acid)] , CP, PC, PVA
	Electrostatic interaction	Chitosan

Evaluation of Buccoadhesive Dosage Form:

(A) In vitro / Ex vivo methods:

The most commonly employed in vitro techniques are:

(i) Methods based on measurement of tensile strength

(ii) Methods based on measurement of shear strengths

Other in vitro methods are

i. Adhesion weight method
ii. Colloidal gold staining method
iii. Fluorescent probe method
iv. Isometric method.
v. Flow channel method
vi. Thumb method
vii. Mechanical spectroscopic method
viii. Adhesion number
ix. Falling liquid film method
x. Electrical conductance

(B) In vivo methods:

The most common in vivo techniques to monitor bioadhesion include:

i. Use of radioisotopes
ii. Use of Electron paramagnetic resonance (EPR) oximetry
iii. Use of gamma scintigraphy Isolated loop technique
iv. Use of pharmacoscintigraphy X-ray studies

Buccal Permeation studies: [11]

Before a buccal drug delivery system can be formulated, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the drug candidate. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

1. In vitro Methods:

Presently, most of the in-vitro studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the in-vitro permeation experiments.

Some Marketed Product of Buccal Tablets:

Table No. 4: Some Marketed Product of Buccal Tablets

S.No	Brand Name	Drug	Company
1	ACTIQ	Fentanyl(100,200,400,600, 800 microgram)	Cephalon (UK) Ltd.
2	ACTIQ	Fentanyl Citrate (100,200, 400, 600,800,1200,1600 microgram)	Flynn Pharma Ltd .
3	BUCCASTEM	Prochlorperazine maleate (3 mg)	Alliance Pharmaceutical, Wiltshire
4	EFFENTORA	Fentanyl(100,200,400,600,800 microgram)	Cephalon (UK) Ltd .
5	FENTORA	Fentanyl(100,200,400,600,800 microgram)	Cephalon (UK) Ltd .
6	LORAMYC	Miconazole(50 mg)	TherebelPharma UK Ltd
7	STRIANT	Testosterone(30 mg)	Columbia Laboratories
8	STRAINT SR	Testosterone(30 mg)	TheUrologyCompanyLtd
9	SUSCARD	Glyceryl trinitrate(2,3,5 mg)	Forest Laboratories(UK) Ltd .

Future Prospective & Conclusion:

There are only a few mucoadhesive formulations available currently, it can be concluded that drug delivery using mucoadhesive formulations offers a great potential both for systemic and local use in the near future. There is no doubt that the oral route is the most favored and probably most complex route of drug delivery. Critical barriers such as mucus covering the GI epithelia, high turnover rate of mucus, variable range of pH, transit time with broad spectrum, absorption barrier, degradation during absorption, hepatic first pass metabolism, rapid luminal enzymatic degradation ,longer time to achieve therapeutic blood levels, and intrasubject variability, are all possible issues with oral route. The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. Therefore a primary objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing. New and unforeseen challenges are expected in the use of mucoadhesives for the delivery of new drugs and in the search of ideal mucoadhesives. Efforts have to be made to develop standardized *in vitro* and *ex vivo* biological models that allow one to characterize and compare different material and formulation in terms of their capability to promote drug absorption via the buccal route.

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How to cite this article:

Tarun Virmani et al.,: Buccal Drug Delivery system- Approach to Improve the Bioavailability, J. Pharm. Res., 2015; 4(5): 220-225.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil