

Brief Emphasis on Mucoadhesive Patches

VR. Tagalpallewar*, AG. Moon, DD. Kakarwal, MB. Wawre and NH. Indurwade

Department of Pharmaceutical chemistry, Dr. R.G. Bhoyar Institute of pharmaceutical Education & Research, Maharashtra, India.

ABSTRACT

Buccal drugs delivery provides an attractive alternative to the oral route of drug administration. The mucosa has a rich blood supply and provides rapid absorption for drugs. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion. The substrate possessing bioadhesive polymer can help in drug delivery for a prolonged period of time at a specific delivery site. Both natural and synthetic polymers are used for the preparation of mucoadhesive buccal patches. Various natural polymers which can be used in mucoadhesive buccal patches are chitosan, sodium alginate, tragacanth, gelatine and guar gum etc. The patches were evaluated for their physical characteristics like mass variation, drug content uniformity, folding endurance, surface pH, and *in vitro* drug release, *in vitro* buccal permeation study, ex vivo bioadhesion strength and ex vivo mucoadhesion time.

Keywords: Mucoadhesion, mucoadhesive polymer, manufacturing methods.

INTRODUCTION

The pharmaceutical industry has been considerable interest making it a major part in the healthcare industry. pharmaceutical industry have greatly contributed in terms of treatment of disease, thereby enhancing the quality of life. Over the time, scientists and researchers in the drug development industries are mainly targeting on alternate routes¹. Amongst various routes of drug delivery, an oral route is perhaps the most preferred to the patient and clinicians alike. However these routes present some problems of few drugs. The enzymes in the GI fluids and pH condition few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drugs directly to the liver leading to first pass metabolisms resulting poor bioavailability. In case other route rectal, vaginal, sublingual and nasal low patient compliance. The inherent problem associated with in some drug, can be solved by modifying the formulation. There are the need alternative routes for the systemic drug delivery drugs². Buccal routes of drug delivery offer various advantages over conventional drug delivery. These advantages include possible by pass of first pass effect, avoidance of pre-systemic elimination within the GI tract, these factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. The buccal mucosa has rich blood supply and it is relatively permeable.

Oral mucosal route

Oral mucosal drug delivery of drugs is classified into three categories.

1) Sublingual delivery

Is the administration of the drug via the sublingual mucosa (under site of the tongue and the floor of the mouth) to the systemic circulation.

2) Buccal delivery

The administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.

3) Local delivery

The delivery of drug in to oral cavity.

Advantages of buccal drug delivery³

- Bypass of the gastrointestinal tract environment, increasing the bioavailability.
- Improved patient compliance due to the elimination of associated pain with injections and tablet.
- A relatively rapid onset of action can be achieved relative to the oral route
- The formulation removed in case emergency condition.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Nausea and vomiting are greatly avoided by buccal drug delivery.

- Used in case of unconscious and less co-operative patients.

Disadvantages buccal drug delivery systems

- Drugs cannot be formulated which irritate oral mucosa.
- During time of treatment buccal drug delivery patient cannot eat and speak.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Swallowing of saliva can also potentially lead to the loss of Drug.

Overview of the oral mucosa

Structure

The oral cavity consists of two regions, the outer oral regions which is made by the cheeks, lips, teeth and gingiva (gums) and the oral cavity proper which extends from the teeth and gums back to the fauces (which lead on to the pharynx) with the roof consisting the hard and soft palates. The buccal mucosa refers to the membrane lining the inside of the cheek is called as "buccal drug delivery" refers to outer regions. In mouth the outermost layer of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria and overlying a submucosa containing blood vessels and nerves. See fig.1. The mucosa can be divided into three parts the masticatory mucosa, lining mucosa, specialised mucosa. Masticatory mucosa was found on the gingiva and hard palate.

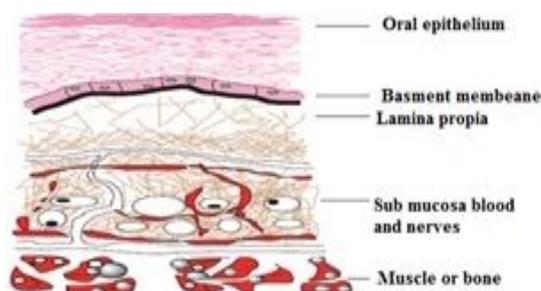


Fig. 1: Cross section area of oral mucosa

The lining mucosa found on the lips, cheek, and floor of the mouth, under surface of the tongue and the soft palate and the specialised mucosa found on the upper surface of the tongue and parts of the lips See fig1. The epithelia is similar to squamous stratified epitheliums found in rest of body consist of cell layers thick (40-50 for the buccal mucosa). In

the case of the masticatory mucosa the outer layers are keratinised may be said to be similar (but not identical) to skin. The total surface area of the oral mucosa is about 100 cm² and the buccal mucosa makes up about a third of this. Generally the non-keratinised mucosae tend to be thicker than the keratinised mucosae. The buccal mucosa is approximately 0.5 mm thick while other mucosae are thinner, i.e. about 0.25 mm.

The main function of saliva

1. Remineralisation of teeth with calcium phosphate salts
2. Neutralization of acid in oral cavity and oesophagus
3. Lubrication and cleansing of the oral
4. Stimulation of epithelial proliferation
5. Initiation of fat and starch digestion

Chemically saliva consists of 99.5% water with 0.5% solutes. The solutes include ion (sodium, potassium, calcium, phosphate, bicarbonate) dissolved gases, urea, uric acid, serum, globulin, mucin and pH of salivary vary from 6.2 to 7.4⁴. The oral cavity contains many sensory receptors including the taste receptor of tongue⁵.

Drug transport mechanism

Drug transport mechanisms in buccal drug delivery two possible routes.

- 1) In case of transcellular route transport of drug inside the cell (passing through the cell)
- 2) The par cellular route transport of drug outside the cell (intercellular passing around the cell)

Design of buccal Drug delivery

A. Matrix type

In case of matrix design of buccal drug delivery contain drug and additives mixed together.

B. Reservoir type

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

Basic component of buccal buccal drug delivery³

1. Drug substance

The selection of suitable drug for the design of mucoadhesive drug delivery systems should be based on pharmacokinetic properties.

1. The drug should have following characteristics.
2. The dose size of drug should be small because small surface area of buccal region
3. The drugs having biological half-life between 2-8 hours are good

candidates for controlled drug delivery.

4. T max of the drug shows wider-fluctuations or higher values when given orally.
5. The conventional drug delivery drug show first pass effect.
6. Absorption mechanisms of drug should be passive.

2. Bioadhesive polymer⁷

First step in the development of mucoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation. Bioadhesive polymers play a major role in mucoadhesive drug delivery systems of drugs.

Natural-Semi natural polymer

Agarose, chitosan, gelatine, Hyaluronic acid various gums.

Cellulose derivatives

CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC.

Synthetic polymer

poly (isobutylycyanoacrylate), copolymer of acrylic acid and PEG.

Others

PVA, PVP thiolated polymers.

Backing membrane

Backing membrane plays a major role in mucoadhesive drug delivery. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include Carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil, ethyl cellulose. Etc

Permeation Enhancers

Penetration enhancers are the substances, which improve the buccal mucosal membrane permeation rate. Although most 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 with the rapid development of biotechnology, more and more protein, peptide, an nucleotide drugs are becoming available, most of which have low membrane-absorption.

Mucoadhesion⁸

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment of a polymer is to mucus or a mucous membrane, the phenomenon is known to as Mucoadhesion

Theories of mucoadhesion

Diffusion Theory

According to diffusion theory polymer chains and mucin mix together sufficient depth to form semi-permanent bond. Depth of semipermanat bond depends on diffusion coefficient, time of contact, and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as the cross- linking density increases. The molecular weight, chain flexibility, expanded nature of both the mucoadhesive and substrates as well as similarity in chemical structure are required for good mucoadhesion.

Electronic theory

In this theory electron transfer occurs on contact of adhesive polymer and the mucus glycoprotein network because of difference in their electronic structure. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

Table 1: Penetration Enhancer used buccal drug delivery¹

| | |
|------------------------------------|---|
| Surfactant | Ionic Sodium lauryl sulphate cetyl ether, Laureth-9 Non-ionic Tween 80, Polysorbates Sodium glycocholate |
| Bile salts and derivatives | Sodium deoxycholate, Sodium taurocholate, Sodium taurodihydrofusidate(STDHF) |
| Fatty acids and derivatives | Oleic acid, Caprylic acid, Oleic acid Mono(di)glycerides, Lauric acid, Linoleic acid, Sodium caprate |
| Chelating agents | EDTA, Citric acid, Salicylates |
| Sulfoxide | Dimethylsulfoxide(DMSO), Decylmethyl sulfoxide |

Fracture Theory

The fracture theory of adhesion is related to separation of two surfaces after adhesion.

Adsorption Theory

According to this theory, after an initial contact of two surfaces the material will adhere because of surface forces two type of chemical bond Primary chemical Bonds mainly covalent bond and Secondary chemical bond having different force of attraction, electrostatic forces of attraction, Vander wall forces of attraction.

Manufacturing Methods of buccal patch⁹

1. Solvent casting

In this method water soluble polymers are mixed water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

2. Semisolid casting

Semisolid casting method firstly a solution of water- soluble film forming polymer is prepared. This solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

3. Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion. ⁽¹¹⁾Advantages of hot melt extrusion. The advantages of hot melt extrusion is 1) Fever operation 2) unit 3) Better content uniformity 4) An anhydrous process

4. Rolling Method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and size.

In Vitro methods

1. Beaker methods

In these methods the dosage form is made adhere at the bottom of the beaker containing the medium and uniformly using overhead

stirrer. Volume medium used in the literature for the study varies form 50-500 ml and stirrer speed from 60-300rpm¹³. Many laboratory animals have been tested for *In vitro* oral mucosa permeability studies. The most commonly used animal are dogs, rats, rabbits, hamsters, pig, monkey are believed to be similar oral mucosa because the epithelia non keratinized.¹⁴ *In vitro* permeability coefficient of titrated water in human and pig oral mucosa, buccal and floor of mouth have been reported to be similar¹⁵.

2. Dissolution apparatus

Standard USP or BP dissolution apparatus have been to study in vitro release profiles using both rotating element paddle, and basket. Dissolution medium for study varied from 100-500 ml and speed rotation from 50-100 rpm.¹⁶

3. Other methods

other methods involve plexiglass sample blocks place in flask agar gel methods, valia-chien, USP type dissolution apparatus etc although a number of methods have been reported, the ideal methods would be one where sink condition is maintained and dissolution time *in vitro* simulates dissolution time *in vivo*.

4. In vivo methods

The most desirable in vivo approach is to perform experiment in human volunteers or patient. However, it is very difficult to begin with this approach because of the difficulties of cost, time, and toxicity of drug and ethical consideration. Therefore, animal models are being usually used for this purpose. The most important and difficult aspect of experimental design is the choice of the animal species. Animal models such as dogs, cat, rabbit, rat, sheep, have been used to determine the oral mucosal absorption characteristics of drugs. Very few, and certainty no extensive in vivo animal in vivo human correlation have been reported, which would allow us to compare the oral mucosal absorption characteristics of a particular animal with those of its human counterpart. However, the methods used in vivo studies are absorption cell and perfusion cells.

5. Disc methods

These methods have advantage that the absorption across a defined oral cavity mucosa can be studied. A polymer disc with a diameter of approximately 3.5 cm and height of 1 cm was used in a study. The disc had a central depression depth of 4 mm. A water

soaked filter paper disc was placed in the depression and known amount of drug spread onto it. Once the drug had dissolved the device was placed on to defined oral mucosal surface and maintained in place for 5 min. After removal, a non-impregnated disc was used to wipe the oral mucosa, the discs combined and analysed. Disc techniques allow investigation to study drug loss across a fixed area defined oral cavity the membrane. Major limitation of the technique includes adherence of disc to the membrane, leakage of drug from the disc and interference from salivary secretion.

6. Absorption cells

Absorption cells are defined as those techniques which restrict known volumes of an aqueous test solution to a defined area of oral mucosa. The cell can be open or closed in the oral environment, but in either case, the test solution within the cell is protected from salivary and, therefore, volumes does not change. In this methods used a rubber 'o-ring' with an internal diameter of 2.64 mm which was fixed to the mucosa using cyanoacrylate adhesive. The cell was filled with 10 μ l of buffered test solution and the absorption characteristics of the organic solutes were determined by taking plasma samples and samples of the test solution in 'o-ring'.¹⁷ This method involving a "cup" which exposed a surface area of 2.2 cm^2 to investigate absorption characteristics of a novel angiotensin converting enzymes ACE across the buccal mucosa of anesthetized dogs.

7. Perfusion cell for animal studies

Veillard developed perfusion cell which was made from medical grade silicon polymer. The cell had volume of 0.075 cm^3 and exposed area of 0.25 cm^2 . Barshun constructed peliable cell made of hydrophilic vinyl polysiloxane polymer which had an internal volume of 1 ml and allowed a 1.8 cm^2 area of buccal membrane to be perfusion cell design also incorporated sealing lips prevent leaks. Ranthabone reported a buccal perfusion design constructed from flexible material perfusion cells of the types mentioned above offer fixed known interfacial area over which transfer can take place into defined oral cavity membrane. The isolation of area over which transfer occurs prevent interfaces from salivary secretion thus aqueous phase volume pH and temperature of the perfusion remain constant throughout duration of experiment.

8. Human technique

Animal models play important role in the the development of an oral mucosal drug delivery system, but these models are only appropriate to use for the screening of a series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluation a set of formulation if one certain that the route of penetration enhancers or structure and the composition of permeation barrier for both the drug and excipient are an exact mimic of its human counterpart.^[17] Until a suitable animal model is found whose absorption characteristics correlate well with its human Counterpart and in which the route of penetration structure and composition of the permeation barrier are considered, an exact of human oral mucosa the continued refinement of human methodology is of a most important. Accurate measurement of the oral mucosal absorption characteristics of drugs in man is needed for the rational design of a delivery system.

9. Buccal absorption test

one of the simplest and direct, measurements of penetration through the oral mucosa is the buccal absorption test. It was introduced by Backett and Trigs in 1967. The test is the simple, non invasive methods for estimating the rate and extent of drug disappearance from the oral cavity. The methods involves controlled swirling of a buffered drug solution of known concentration around the oral cavity for fixed time and then expelling it out. the difference between the amount of drug contained in the original solution and amount recovered is assumed to be the amount of drug lost into the oral mucosa during the test periods¹⁸.

10. In vivo patch test

In this studied the release of drug from medicated buccal patches of drug using human volunteers. The patches were applied to the upper gums of healthy volunteers and patches were removed at a particular time and dissolved in appropriate solvent/buffer and spectrophotometrically.

Formulation of buccal drug delivery system

1. Tablets

Lozenges, troches and tablets for systemic delivery across the oral mucosa are currently commercially available for drugs including nitro-glycerine and fentanyl. Solid formulations such as tablets and lozenges dissolve into the saliva utilising the whole surface area of the oral cavity for absorption. Drawbacks of tablets and lozenges include variation due to

differences in saliva production and sucking intensity, accidental swallowing and short exposure time, usually no greater than 30 min. Mucoadhesive tablet formulations are better in this respect as they adhere to the mucosa-increasing exposure time. One example of this is a mucoadhesive tablet under development shown to deliver therapeutic doses of flurbiprofen to the saliva for 12 h. This mucoadhesive tablet allowed patients to eat and speak without discomfort and caused no irritation, bad taste or pain.

2. Sprays

Glycerol trinitrate is a small molecule that can be rapidly delivered across the. Sublingual oral mucosa using a spray for angina relief. The Generex Oral-lyn™ spray uses micelles and generally recognised as safe GRAS-like surfactants as permeability enhancers to improve the permeability of the drugs across the buccal epithelium.

3. Mouthwashes

The current literature on mouthwashes and oral rinses predominantly focuses on their use in the local delivery of antimicrobial agents. Chlorhexidine gluconate is one such antimicrobial with literature supporting its use in the management of gingival and periodontal disease.

4. Gels

Gels have been investigated as a means of controlled drug delivery since the 1980s. The primary goal of bioadhesive controlled drug delivery is to localise a delivery device within the body to enhance the drug absorption process in a site specific manner.

5. Pastes

The use of pastes as a drug delivery vehicle is a relatively under investigated method with

most current literature focussing on the intracanal delivery of antimicrobial pastes in endodontic; however this is beyond the scope of this review. One currently commercially available mucoadhesive paste is Orabase®.

6. Patches

Several different patch systems that adhere to the oral mucosa and are designed to deliver drugs have been developed. There are basically three different types of mucoadhesive adhesive patches with a dissolvable matrix for drug delivery to the oral cavity. These patches are longer acting than solid forms such as tablets and lozenges and can produce sustained drug release. They slowly and completely dissolve during use leaving nothing to remove. However significant amounts of drug will be lost to the oral cavity. They are better used, therefore, for delivering drugs more generally into the oral cavity than into the oral mucosa to which they are applied. Non-dissolvable backing patches systems for systemic drug delivery that offer protection from saliva.

7. Wafers/films

Thin strips of polymeric films, capable of loading up to 20 mg of drugs, dissolve on the tongue in less than 30 s and deliver drugs (which are able to cross the permeability barrier) directly to the blood supply for rapid treatment of conditions such as impotence, migraines, motion sickness, pain relief and nausea. Similar wafer technology is already used in the treatment of migraines and it is hoped the fast dissolution of the wafers, the self-administrable nature of the technology and the high blood supply of the oral mucosa will enable fast effective treatments for many more conditions in the future.¹

Table 2: examples of drugs with oral or transmucosal delivery routes¹¹

| Delivery formulation | Generic name | Commercial name | Marketing company | Indication description |
|----------------------|--|-----------------|--|--|
| Tablet | Fentanyl buccal | Fentora™ | Cephalon, Inc, USA | Breakthrough cancer pain |
| Lozenge | Oral transmucosal fentanyl citrate lozenge | Actiq | Teva pharmaceutical USA | On maintains of opioids pain |
| Wafer/film | Fentanyl buccal dissolvable film | Onsolis | Meda pharmaceutical | cancer pain |
| Spray | Insulin mouth spray | Oral-lyn™ spray | Multiple international marketing companies | treatment of Type I and Type II diabetes |
| Gel | Bioadherent oral gel | Gelclair® | EKR Therapeutics, Inc, Bedminster, | Management pain in mouth |

REFERENCES

1. Verma S, Kaul M, Rawat A and Saini S. An overview on buccal drug delivery systems. *Int J pharm sci and Res.* 2011;2(6):1303-1321.
2. Jain NK. *Controlled and novel drug.* 1st edition new Delhi CBS publication, 2002;52.
3. Gandhi P, Patel K and Patel N. A review article on mucoadhesive buccal drug delivery systems *Int J pharm Res and Dev.* 2011;3:159-173.
4. John D Smart. *Drug delivery using buccal-adhesive systems* Advanced Drug Delivery Reviews. Elsevier Science Publishers. 1993;253-270
5. Patel V and Liu F. M. Brown. *Advances in oral transmucosal drug delivery review.* *J Cont Rel.* 2011;153:106-116
6. Lam K and Henk T. buccal drug delivery: A challenge already won? *Drug Discovery Today: Technologies | Drug delivery/formulation and nanotech.* 2005;1:59-65
7. Miller N, Chittchang M and Thomas J. The use of mucoadhesive polymers in buccal drug delivery *Adv. Drug Delivery Reviews* 2005;57:1666-1691.
8. Parthasarathy G, Bhaskar K, Jayaveera K and Prasanth V. Buccal Mucosa: Gifted Choice for Systemic Drug Delivery. *Int J Drug Delivery.* 2011;3:586-596.
9. Arya A, Chandra A, Sharma V and Pathak K. Fast Dissolving Oral Films: An Innovative Drug. *Int J Chem. Tech Res.* 2010;2:576-583.
10. saurbh R, Malviya R and Kumar Sharma P. Trend in buccal film formulation and characteristics recent studies and patent *Euro J applied sci.* 2011;3:93-101.
11. Hearnden V, Sankar V, Hull K, Juras D, Martin G Ross Kerr, Peter Lockhart, Lauren Patton, Stephen Porter and Martin Thornhill. New developments and opportunity in oral mucosal drug delivery for local and systemic disease. *Adv Drug Del Rev.* 2012;64:16-28.
12. Amir HS. Buccal mucosa as a route for systemic drug delivery. *Rev J pharma pharmaceu sci* 1998;1:15-30
13. Udupa T. preparation and evaluation of buccal dosage form insulin. *Pharmag.* 1995;4:8-14.
14. Launa P, Fausta A and Maurizio R. development of mucoadhesive patches for buccal administration of ibuprofen. *J cont Rel.* 2001;77:253-60.
15. Silvia R, Giuseppina S and acrla MC. Buccal drug delivery: A challenge already won? *Drug delivery today.* 2005;2:59-65.
16. Thimmasetty J, Pandey G and Sathesbhabu PR. Design and in vivo evaluation of carvedilol buccal patch. *Pak J pharm Sci.* 2008;21:214-218.
17. Veillard, longe, martens and Robison. Preliminary studies of oral mucosal delivery of peptide drugs. *J cont Rel.* 1987;6:123-31.
18. Rathbone MJ and Hadgrft J. Absorption of drug from the human oral cavity. *Int J pharm.* 1991; 74:9-24.
19. Beckett AH and Triggs EJ. Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membrane. *J pharma pharmacol.* 1967;19:31-34.