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Mucoadhesive Buccal Films: An Innovative Drug Delivery System

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Abstract: Buccal drug delivery is the most innovative delivery system which releases the drug to buccal mucosa by avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. The buccal mucosa has a rich blood supply and local environment of the mucosa can be controlled by an exact dosage form in order to optimize drug dissolution and permeation. Mucoadhesive buccal films are retentive dosage forms that release the drug directly into the biological substrate. These films are light in weight and releases topical drugs in the oral cavity at a slow and predetermined rate, provide discrete advantages over traditional dosage forms for treatment of many diseases. This article aims at reviewing advantages of films, manufacturing process, various polymers and its evaluation parameters.
Keywords: Buccal mucosa, first-pass metabolism, mucoadhesive buccal film, drug dissolution, retentive dosage form.

Introduction

Oral route is the most common convenient and preferred route when compared to other routes of delivery of drugs. Delivery of drug via buccal route is considered to be a foremost choice to the oral and parenteral routes of systemic drug delivery.[1]The buccal mucosa is relatively permeable and provides affluent blood supply.[2] and permits a prolonged retention of a dosage form, especially with the use of mucoadhesive polymers without much interference in processes such as mastication unlike the sublingual route.[3] The array of permeability of the oral cavity is given as Sublingual>buccal>palatal. Administration of the drug via the mucosal layer is a novel technique that delivers treatment more effective and safe, for both topical and systemic diseases.[4, 5]

Over the last two decades, mucoadhesion gains major interest for its potential to optimize localized drug delivery because it only retains a dosage form at the site of action (with in the gastrointestinal tract) but also keeps the formulation in intimate contact with the absorption site (in the buccal cavity).[6] The concept of mucoadhesion has gained significant concern in pharmaceutical technology in the early 1980s.[7]

Adhesion is a process defined as the ‘‘fixing” of two surfaces to each other.[8] Bioadhesion is stated as the process in which two materials, one of which is natural in origin, are held mutually for extensive periods of time by means of interfacial forces. This phenomenon is referred to as mucoadhesion in which to a mucous membrane the adhesive is attached. [9]

Overview of the Oral Mucosa

The oral cavity covers the cheek, lips, tongue, hard palate, soft palate and floor of the mouth (Fig-1). The lining of the oral cavity is referred to as the oral mucosa. Numerous mucous or serous glands are seen in the sub mucous tissue of the cheeks. The buccal, sublingual and the mucosal tissues on the ventral surface of the tongue covers for about 60% of the oral mucosal surface area. The one-third of the oral mucosa is made up of closely compacted epithelial cells. Beneath the epithelial layer are the basement membrane, lamina propia and submucosa. [10]

Table No - I: Oral mucosa in the oral cavity is divided as follows.

Oral mucosa types	Present in	Epithelium	Layers	% covering total oral cavity
Lining mucosa[11,12]	Lips, cheeks, soft palate and lower surface of the tongue.	Non-keratinized stratified squamous epithelium	• Basal layer • Intermediate layer • Superficial layer	60%
Specialised mucosa	Dorsal surface of tongue.	Both keratinized and non keratinized epithelium	——	15%
Masticatory mucosa. [13]	Hard palate (the upper surface of the mouth) and the gingiva (gums).	Keratinized stratified squamous epithelium	• Keratinized, • Granular, • Prickle-cell • Basal layers.	25%

The superficial cells of the masticatory mucosa are keratinized. The soft palate, buccal and the sublingual regions of the macros are not keratinized while the mucosa of the gingival and hard plate are keratinized.[14] The non–keratinized epithelia are more permeable to water than the keratinized epithelia.[15]

Mechanism Of Mucoadhesion

Mucoadhesion mechanism of is mainly divided in two steps.

1. The Contact Stage: involves intimate contact between a mucoadhesive and a membrane (wetting or swelling phenomenon). [4, 10]

2. The Consolidation Stage: involves penetration of the mucoadhesive into crevices of the tissue or into the surface of the mucous membrane (interpenetration). [4, 10]

Advantages of Mucoadhesive Drug Delivery [16]

- Rapid onset of action.
- The drug is easily administered by buccal delivery that is unstable in acidic environment of the stomach.
- Avoidance of first pass metabolism and thereby increase in bioavailability.
- Due to the intimate contact surface of the oral cavity with mucoadhesive membrane, maximized absorption rate occurs.
- The drug release is prolonged for a certain period of time.
- Flexibility in designing as multi or unidirectional release systems not only for local but also systemic actions.
- The thin film is more stable and durable than other conventional dosage forms and also improves dosage accuracy relative to liquid formulations.

Limitations of Mucoadhesive Drug Delivery[17]

- Drugs that have a disagreeable taste or irritate the mucus cannot be administered.
- Drugs that are in an unstable environment at buccal pH cannot be administered.
- Drugs causing allergic reactions, discoloration of teeth cannot be formulated.
- Buccal mucosa has low permeability when compared to the sublingual mucosa.
- Drug with large dose cannot be administered.
- To local action the rapid elimination of drugs due to the flushing action of saliva may lead to the requirement for frequent dosing. [18]

Mucoadhesive Delivery Devices [19 - 26.]

Solid buccal adhesive dosage forms

- Tablets
- Micro particles
- Wafers
- Lozenges

Semi solid buccal adhesive dosage forms

- Gels
- Patches/films

Liquid buccal adhesive dosage form

- Viscous liquids

Mucoadhesive Buccal Films

Various mucoadhesive devices has been formulated like tablets,[27] patches,[28] devices,[28] strips,[29] ointments,[30] gels, [31] disks.[32] and more recently films.[26] Films can circumvent the difficulty of the relatively short residence time of oral gels on mucosa because the gels are easily washed away by saliva.[33] An ideal buccal film must be soft, flexible, expandable and strong enough to withstand breakage because of stress from activities in the mouth and also it possess good mucoadhesive strength so that can be retained in the mouth for the desired duration.[24]

Films are fabricated to cause a systemic or local action since mucoadhesion implies attachment to the buccal mucosa. [34] Most of the mucoadhesive buccal films have been formulated in order to treat fungal infection in the oral cavity such as oral candidiasis which releases the drug locally. [35]

Methods of Manufacture of Mucoadhesive Buccal Films

The main manufacturing processes involved in mucoadhesive buccal films are as follows:

1. Solvent casting
2. Hot-melt extrusion

1. Solvent Casting[26, 36- 40]

In this method, the drug and excipients is dissolved in appropriate solvent and water soluble polymers are dissolved in water and these solutions are stirred and at last casted into the petri plate and dried.

Steps in film casting

API and other excipients are dissolved in appropriate solvent to form a clear viscous solution

↓

The formed solutions are mixed

Then, solution is cast as a film and allowed to dry

↓

Film is collected

Hydroxy propyl methylcellulose (HPMC), Hydroxy propyl cellulose (HPC), sodium alginate, pullulan and pectin are the water soluble hydrocolloids used to prepare films .

2. Hot-Melt Extrusion[41- 43]

Rebekah *et al* has performed research on the use of this method for the manufacture of mucoadhesive buccal films, evaluating different matrix formers and additives for the processing of the blend. They also determined and compared the bioadhesive profiles of hydroxyl propyl cellulose (HPC) polymer matrices as a function of Δ^9-tetrahydrocannabinol (THC) content by using this method.[44]

Steps in Hot-melt extrusion:

In dry state drug is mixed with carriers

↓

Extrude via heating melts the mixture

↓

The mass is cast in the films by the die.

Mucoadhesive Polymers

Mucoadhesive polymers are either water soluble or insoluble, derived from natural or synthetic source and are able to form several hydrogen bonds because of the presence of carboxyl or hydroxyl Functional groups.[45]

Ideal Properties of Mucoadhesive Polymers [46, 47.]

It must assure the following properties.

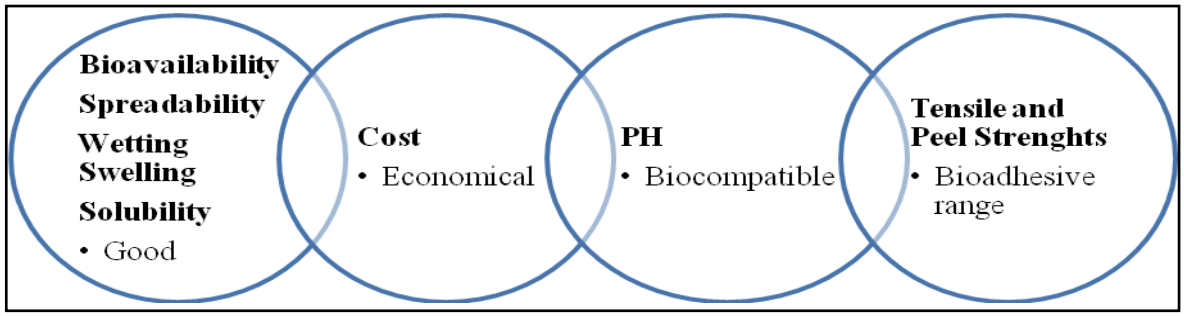

Fig - 1: Schematic representation of Ideal Properties of mucoadhesive polymers

Mucoadhesive Polymers are classified as follows [48-52.]

1. NATURAL POLYMERS

1. Protein based polymers: albumin, gelatin, collagen
2. Polysaccharides: Alginates, Starch, Cellulose, Cyclodextrines, Chitosan, Dextran, Agarose.

2. SYNTHETIC POLYMERS

Biodegradable polymers

1. Polyesters: Polyglycolic acid, Polylactic acid, Polyhydroxyl butyrate, Polycaprolactone, Poly Doxanones.
2. Polyanhydride: Polyterphthalicacid, Polyadipic acid, Polysebacic acid.
3. Polyamides: Poly amino acids, Poly iminocarbonates.
4. Phosphorous Based polymers: Polyphosphates, Polyphosphazenes, Polyphosphonates.
5. Others: Poly cyanocrylates, Poly urethanes, Polyorthoesters, Polyacetals.

Non biodegradable polymers

1. Cellulose derivatives: Carboxy methyl cellulose, Ethyl cellulose, Cellulose acetate HPMC.
2. Silicones: Colloidal silica, Polydimethyl siloxanes, Polymethacrylates
3. Others: PVP, EVA, Poloxamines.

Novel Mucoadhesive Polymers

a) Lectins

These are naturally occurring proteins that play an important role in biological recognition phenomena involving cells and proteins.

Table No - II: Lectins can be divided into three types based on molecular structure

Type of Lectin	Number of domains
Merolectins	One (carbohydrate recognizing)
Hololectins	Two or more (carbohydrate recognizing)
Chimerolectins	Additional (unrelated)

The use of lectins for targeting drugs to tumor tissue is currently under intensive investigation as the human carcinoma cell lines exhibit higher lectin binding capacity than the normal human colonocytes.

b) Thiolated polymers

These are hydrophilic macromolecules belongs to the special class of multifunctional polymers called thiomers by the addition of thiol group existing polymers are modified. Various thiolated polymers include poly(acrylic acid)–cysteine, Chitosan–thioglycolic acid, poly(acrylic acid)–homocysteine,chitosan–thioethylamidine,alginate–cysteine,and sodium carboxymethylcellulose–cysteine.[53]

c) Alginate-polyethylene glycol acrylate (alginate - PEGAc)

This is a novel mucoadhesive polymer, synthesized in which an alginate backbone carries acrylated polyethylene glycol.

d) Poloxomer

Phase transitions are exhibited by poloxomer gels from liquids to mucoadhesive gels at body temperature and will therefore allow in-situ gelation at the site of interest.

e) Pluronics and combination

Pluronics are combined chemically with poly (acrylic acid) s to produce systems with enhanced adhesion and retention in the nasal cavity. Eg. Dihydroxyphenylalanine (DOPA), an amino acid found in mussel adhesive protein combined with pluronics to enhance their adhesion.

Permeation Enhancers

Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. [54] Penetration enhancement to the buccal membrane is drug specific. [55]

Ideal Properties of Permeation enhancers

- Should be inert, non toxic, non irritating and non allergenic.
- Should be pharmacological and chemically inert. [56]
- Should be compatible with both excipients and drugs.

Table No - III: Examples of different permeation enhancers [56-58].

Type	Examples
Chelators	EDTA, Sodium salicylate, Citric acid, Methoxy salicylates.
Surfactants	Sodium Lauryl Sulphate, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, Polyoxyethylene, Cetylpyridinium chloride, 23-lauryl Ether.
Non-surfactants	Unsaturated cyclic ureas
Fatty acids	Lauric acid, Oleic acid, Capric acid, Methyl oleate, Phosphatidylcholine
Bile salts	Sodium gtlycocholate, Sodium deoxycholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate, Sodium taurocholate etc.
Inclusion complexes	Cyclodextrins
Others	Aprotinin, azone, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various Alkyl glycosides.

Methods For Mucoadhesion Testing

i) A direct-staining method

This method was used to evaluate the mucoadhesion of polymeric aqueous dispersion on buccal cells by binding alcian blue to anionic polymers and eosin to the amine groups in polymers. Unbound dye was removed by washing with 0.25M sucrose. This method is only appropriate for assessing the liquid dosage forms that are extensively used to enhance oral hygiene and to treat local disease conditions of the mouth such as oral candidiasis and dental caries.[59]

ii) A lectin-binding inhibition technique

It involves the binding of mucoadhesive polymers to buccal epithelial cells without having to vary their physicochemical properties with the addition of ‘‘marker’’ entities.[60] The lectin from Canavalia ensiformis (Concanavalin A) has been bound to sugar groups present on the surface of buccal cells. [61]

iii) Atomic force microscopy

It was used to determine the mucoadhesion of polymer onto the buccal cell surfaces. [62]

Table No - IV: Changes in surface topography results as follows

Unbound cells	Polymer bound cells
Smooth surface	Rough surface
Small crater like pits are seen	Lost
Indentations spread over surfaces	Lost

Evaluation of Mucoadhesive Buccal Films

Film Weight and Thickness[63]

The weight of each prepared film was measured using a digital balance among the three films of every formulation and the average weight was calculated. Similarly the thickness of each film was measured using a micrometer screw gauge at different points of the film and the average was calculated.

Folding Endurance

Folding endurance of the films was premeditated by repeatedly folding one film at the same place till it broke or folded up to 300 times manually The number of times the film could be folded at the same place without breaking or cracking gave the value of folding endurance.[64]

Surface PH

Surface pH of the films can be determined by allowing three films of each formulation to swell for two hours on an agar plate surface. pH was measured by means of pH paper positioned on the surface of the swollen film and a mean was calculated.[65]

Swelling Index[66]

The films were weighed individually and placed on the surface of an agar plate kept in an incubator maintained at 37±0.2°c and the samples were allowed to swell. An increase in the weight of the film was noted in regular intervals of time and the weight was calculated. The percent swelling, %S was calculated using the following equation:

Percent Swelling (%S) = $(X_t - X_o / X_o) \times 100$
Where X_t = the weight of the swollen film after time t,
X_o = the initial film weight at zero time.

Moisture Content

The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. After a specified interval, the films are to be weighed again until they show an unvarying weight. The % moisture content was calculated

By using the following formula.[67]

$$\% \text{ moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Water Vapour Transmission Rate (Wvt) [68]

About 1 g of calcium chloride was taken in the vial which is used as transmission cell and the polymeric films measuring 2 cm^2 area were fixed over the brim with the help of an adhesive. The initial weight of the cells was noted by weighing them accurately. Finally, they are placed in a closed desiccator containing saturated solution of potassium chloride and were taken out and weighed at standard intervals. The water vapour transmitted rates were calculated by using the following formula.

W V T = WL/S
Where, W = water vapour transmitted in mg.
L is the thickness of the film in mm.
S is exposed surface area in cm^2.

In- Vitro Release Study

Dissolution studies are carried out in a USP dissolution apparatus using 900 ml of dissolution medium at 37 ± 0.5ºC, rotated at constant speed of 50 rpm. An aliquot of the sample is periodically withdrawn at suitable time intervals and the volume is replaced with fresh dissolution medium. The sample is analyzed at

specified nm by UV-visible spectrometer spectrophotometrically and amount of drug release at various time intervals were calculated.[69 -71.]

In-Vitro Residence Time

The *in vitro* residence time is performed using IP disintegration apparatus maintained at a temperature of 37 ± 2°C using 900 ml of the disintegration medium. The portion of the rat intestinal mucosa, each of 3 cm length, is glued to the glass piece surface, which is then vertically attached to the apparatus. The films of each formulation are hydrated on one surface and up on contact with the mucosal membrane, the film is entirely dipped in the buffer solution. The time required for complete detachment of the film from the mucosal surface is to be noted.[72]

Ex Vivo Mucoadhesive Strength

The force required to detach the attachment of mucoadhesive film from the mucosal surface was applied as a measure of the mucoadhesive strength. A modified balance method was used for determining the ex-vivo mucoadhesive strength. The porcine buccal mucosa was taken and the mucosal membrane was separated by removing the underlying fat tissues. The mucosa was attached to a dry petri dish surface and it was moistened with a few drops of simulated saliva. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5 g (w_1) was removed from the left pan and film was brought in contact with pre moistened mucosa for 5 min. Then weights were increased lightly on the left pan until the attachment breaks (w_2). The difference in weight (w_2-w_1) was taken as mucoadhesive strength. [73]The mucoadhesive force was calculated from the following equation:

$$\text{Mucoadhesive force (Kg/m/s)} = \frac{\text{Mucoadhesive strength (g)}}{1000} \times \text{acceleration due to gravity (9.8 m/s-1)}$$

Tensile Strength

It is defined as the resistance of the material to a force tending to tear it separately [74 – 82] and is identified as the maximum stress in the stress–strain curve.It was determined using an Instron universal testing instrument with a 5-kg load cell. Films were held between two clamps positioned at a distance of 3 cm and were pulled by the top clamp at a rate of 100 mm/m; the force and elongation were measured when the film broke. It was calculated by the replicate of 3 times. It is given by the following equation.[19]

Tensile strength = Force at break (N) / Cross-sectional area of the film (mm^2).

Percent Elongation Break

The elongation at break is a measurement of the maximum deformation the film can undergo before tearing apart. It is calculated using the following equation.

Elongation at break = Increase in length of break / Initial film length x 100

Table No - V: Parameters influencing the polymer [83]

Property Of Polymer	Tensile Strength	Elastic Modulus	Elongation At Break
Soft and weak	Low	Low	Low
Hard and brittle	Moderate	High	Low
Soft and tough	Moderate	Low	High
Hard and tough	High	High	High

Table No - IV: Recent formulations in mucoadhesive buccal films

Drug	Category	Treatment	Polymer	Permeation enhancer	References
Glipizide	Oral hypo glycemic drug	Diabetes	Hydroxy Propyl methyl cellulose(HPMC), Sodim carboxymethylcellulose (SCMC), Carbopol-934P and Eudragit RL-100	Propylene glycol	63
Glibenclamide			Different grades of Hydroxy propyl methyl cellulose	Propylene glycol	84
Ranitidine	Histamine H2-receptor antagonist	Ulcer And Zollinger Ellision Syndrome	Hydroxy propyl methyl cellulose (HPMC)-15 cps	Polyvinyl pyrrolidone.	64
Famotidine			Hydroxy Propyl Methyl Cellulose (HPMC K4M) Carbopol-934P (CP) and polyvinylpyrrolidone-K30 (PVP).	Propylene glycol	85
Miconazole	Imidazole antifungal agent	Oral Candidiasis	Chitosan	Propylene glycol (PG), polyethylene glycol	86
Losartan potassium	Angio tensin II receptor antagonist drug	Hypertension	Hydroxy Propyl methyl cellulose (HPMC) and retardant polymers ethyl cellulose (EC) or Eudragit RS 100.	Propylene glycol	87
Enalapril maleate	(ACE) inhibitor	Hypertension	Sodiumcarboxymethylcellulose, Hydroxy Propyl methyl cellulose, Hydroxyl ethyl cellulose	Polyvinyl pyrrolidone.	88
Diltiazem	Benzothiazepine calcium Channel blocker	Anginapectoris, systemic hypertension and other cardiovascular disorders	Hydroxy Propyl methyl cellulose, Eudragit, Ethyl cellulose	Polyvinyl pyrrolidone.	89
Flufenamic acid	Anti-inflammatory drug	Oral mucosa inflammation	Chitosan, KollicoatIR	Glycerin	90
Meloxicam	Non-steroidalanti-inflammatory drug	Osteoarthritis and rheumatoid arthritis	Sodiumcarboxymethylcellulose, Hydroxy Propyl methyl cellulose, Hydroxyl ethyl cellulose	Glycerin polyethylene glycol	91
Flurbiprofen	Non-steroidal anti-inflammatory drug	analgesic therapy in the oral cavity	Carbopol,SodiumCarboxymethylcellulose, Hydroxy Propyl methyl cellulose,	Polyvinyl pyrrolidone, Polyethylene glycol	92
Amiloride	Potassium sparing diuretic and Antihyper tensive agent	Hypertension and congestive heart failure	Chitosan, HPMCK4M, Carbopol 934,	Polyvinyl pyrrolidone,	93

Ciprofloxacin Hydrochloride	Second-generation fluoroquinolone	Periodontal diseases	(HPMC K4 M)	Glycerin	94
Fluconazole	Triazole antifungal drug	Oral candidiasis	Hydroxypropylmethyl cellulose, Carbopol 974P, EudragitN30D, Chitosan, ethyl cellulose, Hydroxyethyl cellulose	Propylene glycol	95
Valdecoxib	Selective cyclooxygenase- 2 inhibitor	Oralsub-mucous fibrosis	Chitosan, HPMC K4M	Glycerin	96
Clotrimazole	First line broad spectrum Antifungal agent	Oral candidiasis	Carbopol, Sodium, Carboxylmethyl cellulose	Glycerin	97
Ondansetron hydrochloride	Serotonin 5-HT_3 receptor antagonist	Chemotherapy-induced emesis	(HPMC) E5, HPMC K100, and Eudragit(®) NE 30 D	Propylene glycol	98

Conclusion

Nowadays, a widespread research is being carried out on the progress of the innovative approach of delivery of drug to improve the safety, effectiveness and patient compliance. The buccal mucosa has a rich blood supply and easily accessible, ensuring the application of a dosage form to the required site and removed easily in case of emergency. Mucoashesive buccal films are prepared by reducing the frequency of administration and achieve greater therapeutic efficacy.

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