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Review article

Buccal Mucoadhesive Films: A Review

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ABSTRACT
Traditional oral dosage forms prone to first pass metabolism and degradation due to enzymes but mucoadhesive films able to bypass first pass metabolism and related degradation. It also offers more patient compliance without risk of chocking in case of paediatric and geriatric patients. Present review has summarised basics of mucoadhesion, composition, method of preparation, characterisation parameters, advantages and disadvantages of buccal mucoadhesive films.

Key words: *Buccal, Mucoadhesive* film, Tensile strength, Folding endurance, Solvent casting.

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INTRODUCTION

Drugs are normally administered by following routes through various dosage forms:[1]

Site	Administration	Dosage forms
Oral	Through the mouth	Powders, tablet, capsules, granules, solutions, suspensions, syrups, emulsions
Topical	Skin	Creams, lotions, ointments, gels, solutions, suspensions,
Parenteral	Subcutaneous, intramuscular, intravenous	Solutions, suspensions, emulsions
Trans-mucosal	Nasal, *Buccal* /sublingual, vaginal, ocular and rectal	Tablet, gels, emulsions, films, suppositories
Nasal	Inhalation	Sprays, powders

Oral route is most preferred route of drug administration but solubility and first pass metabolism sensitivity of drug are important characteristic to be accepted by this route. Parental rout is painful drug administration system. Topical drugs are limited for topical or local treatment only.[1]
High molecular weight drugs, poor skin penetrating drugs, poor water insoluble drugs, and extensive first pass metabolism prone drugs need alternative routes. *Mucoadhesive* route is becoming popular alternative for most of the drugs.
Mucoadhesive drug delivery system through *Buccal*, sublingual, rectal and nasal mucosa can be faster and systemic mode of non-invasive drug administration to bypass first pass metabolism. Faster delivery and enhanced bio availability of drugs is observed through *mucoadhesive* administration.[2] Following are various *mucoadhesive* drug delivery systems:

Mucus

A thin, continuous jelly layer of transparent and viscid discharge of epithelial surface is called as mucus made up of glycol proteins located in various body cavities from respiratory and gastrointestinal tract. This mucus layer of thickness of about 50-450 µm in humans actually creates adhesive interface for drugs.[10]
There is continuous secretion of mucus to balance removal of mucus layer during digestion, solubilisation and due to bacteria mediated degradation.[11] Composition of mucus varies according to anatomical locations but overall composition remains as shown in Table 1:

Table 1: Composition of mucus

Sr. no.	Components	Amount (Percentage)
1	Water	90-95
2	Lipids	0.5-6.0
3	Minerals	1-1.5
4	Proteins	0.5-1.5

This mucus layer performs following functions:[12-14]
Protective: allows selective transport and protects epithelial surface from acid diffusion through lumen
Barrier: allows selective absorption for drugs
Adhesion: mucus layer with cohesive properties allows firm adhesion surface for molecules
Lubrication: moisture present in mucus provides lubrication to mucosal layer

Mucus membrane	Surface area	Thickness	Layers	Mucus secretion/ day	Turnover time of mucus
Buccal[2-4]	30 cm	500–800 μm	epithelium, basement membrane, and connective tissues	800-1000 ml	5–6 days
Nasal[5-6]	60 mm	150-200 cm	columnar cells, goblet cells, and basal cells	20 mL	10–15 min
Ocular[2-6]		3–10 µm	epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium	2–3 µL	15–20 h
Vaginal[7-9]	6 to 10 cm	3–10 µm	lamina propia and stratified squamous epithelium	1-4 ml	7 days
Rectal[1,3,9]	300 cm	10–20 cm	Epithelium consists of a single layer of cylindrical cells and goblet cells	3 ml	7 days

Mechanism of mucoadhesion

Contact between a pressure - sensitive adhesive material and a surface is called as adhesion, which can be defined as the state in which two surfaces are attached together due to valence interfacial forces or interlocking action or both. [15-17]

Bio adhesion is an adhesion of a synthetic or natural material to biological surface while mucoadhesion is adhesion of material to mucus and/or an epithelial surface. Mucoadhesion occurs in two stages (Figure 1) depending on nature of dosage form and its delivery:

Stage-I (Contact Stage): wetting, spreading and swelling of the bio adhesive surface creates close contact between a bio adhesive and a membrane. Sometimes additional forces like mechanical system in vaginal delivery, aero dynamics in nasal delivery and peristaltic motions in intestinal delivery of dosage form.[18]

Stage II (Consolidation Stage): moisture breaks molecules and inter penetration or dominant attractive interaction between two surfaces starts due to Vander walls forces, electrostatic attractions, hydrogen bonding and hydrophobic interactions. For complete Bio adhesion attractive forces must overcome repulsive forces. Consolidation step is explained by two theories:[19]

Diffusion theory: mucus glycol proteins interact with the *mucoadhesive* molecules by interpenetrating their chains and forming secondary bonds. This is a chemical as well as mechanical interaction.

Dehydration theory: after contact with mucus, material undergoes dehydration until osmotic pressure balance and gelly mixture of mucus with material is obtained. Solid or hydrated formulation does not work by this theory.[20]

Theories of Mucoadhesion

There are five different theories, which explain phenomenon of mucoadhesion:

Electronic theory

This theory is based on fact that both mucus layer and biological materials have opposing electrical charges that able to create double electronic layer at the edge and thus helps in determination of *mucoadhesive* strength.[21]

Wetting theory

Liquid or less viscous molecules enter into mucosal surface and fix themselves by counteracting the surface tension at the interface. This property relates to contact angle, wetting and spread ability capacity of molecule. (Figure 2) Contact angle (θ) and interfacial tension (γ) can be determined from following equation:[22]

$\gamma SG = \gamma SL + \gamma LG \cos S = \gamma SG - (\gamma SL - \gamma LG)$

Where γLG is liquid–gas surface tension, γSL is solid–liquid surface tension and γSG is solid–gas surface tension.

Diffusion Theory

This theory suggests that *mucoadhesive* polymer diffuses into mucus layer by breaking glycoprotein chain network (Figure 3). This diffusion is time dependent and depends on diffusion coefficients and molecular weight of both phases.[23]

Adsorption Theory

Weak Vander Waals forces and hydrogen bond mediated adhesion involved in adsoption theory is most accepted theory of mechanism of mucoadhesion. It involves primary and secondary bonding in exhibiting semi permanent surface interactions.[24]

Fracture Theory

This is the second most accepted theory, which explains the forces required to detach the two surfaces following adhesion. This force is called as tensile stress or fracture strength and can be determined by following equation:

Sm= Fm/Ao

Where Sm: Tensile stress, Fm: maximum force of detachment andAo: surface area

OR

Sf= (gcE/c) ½

Where Sf: fracture strength, gc: fracture energy (Wr + Wi = work done to produce new fracture surfaces + irreversible work of adhesion), E: Young's modulus of elasticity and c: critical crack length.

Each and every theory (Figure 4) is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

Buccal Drug Delivery

The lip, tongue, cheek, soft palate, hard palate, and floor of mouth comprises oral cavity. Oral mucosal layer consist of three layers: outer epithelium, middle basement and inner connective tissues. 100cm total area of the oral cavity consists of about one third of *Buccal* surface of 0.5mm thickness epithelium.[25]

About 0.5 to 2 litre of saliva runs into oral mucosal surface. P^H of salvia varies between 5.5 to 7 depending on its flow rate. A neutral lipid like ceramides consisting epithelium is keratinized epithelium while polar lipids like cholesterol sulphate and glucosylceramidesis non-keratinized epithelium.[26]

Non-keratinized region of *Buccal* is most suitable region for drug administration especially proteins/peptides than nasal, rectal and vaginal drug delivery. Drug enters into systemic circulation through jugular ducts via network of blood vessels.[27]

Buccal mucosa, lining of cheek and area between the gums and upper and lower lips is most considerable area for drug delivery. It is estimated that the permeability of the *Buccal* mucosa is 4-4000 times greater than that of the skin.

The order of permeability's of the oral mucosa are sublingual >*Buccal*> palatal which depends on relative thickness and degree of keratinization.[28] Outermost 200 μm of the superficial layer consist of barrier of 'membrane coating granules' (MCG) which varies in keratinized and non-keratinized epithelia.

Intercellular spaces and cytoplasm of oral mucosa being hydrophilic acts as a barrier for lipophilic compounds while cell membrane being lipophilic acts as a barrier for hydrophilic compounds.[29]

To overcome this problem of penetration of high molecular weight compounds, absorption efficieny can be enhanced by few chemicals like fatty acids, bile salts and surfactants such as sodium dodecyl sulfate which are called as absorption enhancers.[30]

Characteristics of an Ideal Buccoadhesive System[31-33]

Safe and nontoxic

Sufficient patient compliance without hampering normal functions such as talking, eating and drinking

Good mechanical strength

Immediate adherence to the *Buccal* mucosa

Controlled drug release

Optimum drug absorption

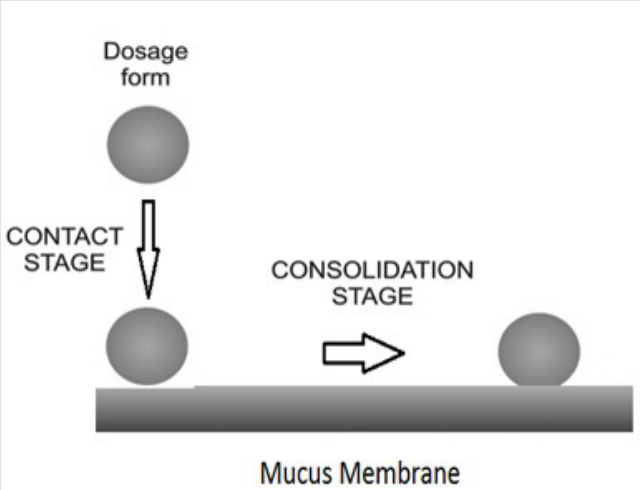

Figure 1: Two steps of Muco-adhesion processes.

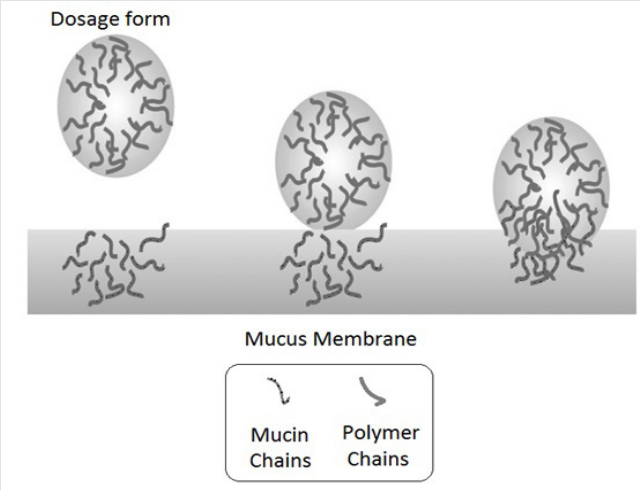

Figure 3: Representation of Diffusion theory.

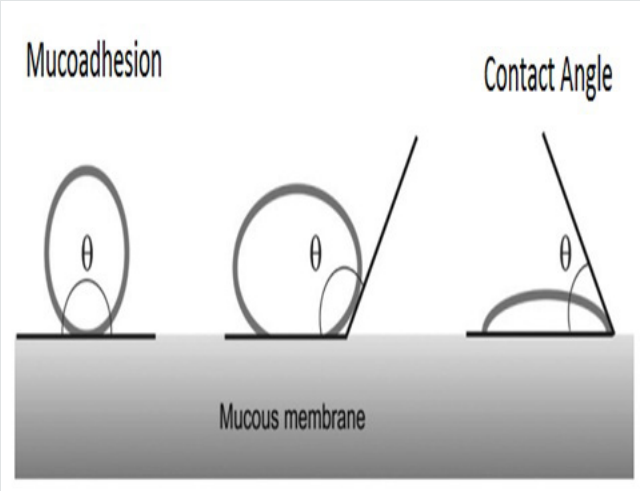

Figure 2: Influence of contact angle in wetting theory.

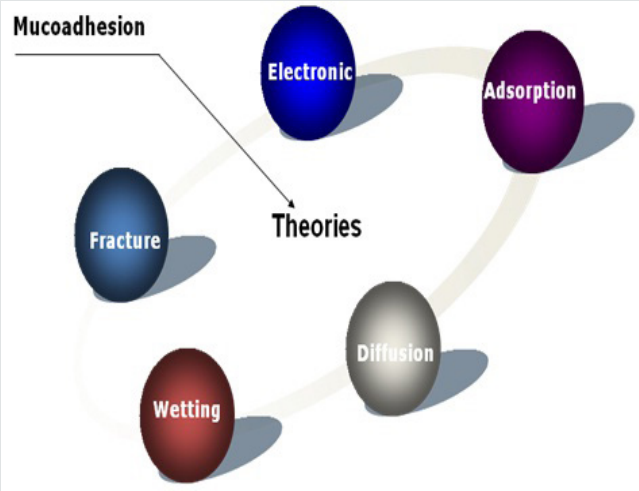

Figure 4: Different mucoadhesion theories.

Advantages of Buccal Drug Delivery System[34-35]

Direct administration of drug into systemic circulation in less time
Avoids the first-pass metabolism and exposure to GIT fluids
Enhanced bio availability due to prolonged contact time with the mucosa
Better patient acceptance compared to other non-oral routes of drug administration
Modification by adding permeability enahncers, protese inhibitors to enhance delivery of high molecular weight compounds like peptides, proteins and ionized species is easy compared to other forms.

Disadvantages of *Buccal* Drug Delivery System[36-38]

Less surface area
Mucosal barrier
Dilution or loss of the drug due to constant secretion of the saliva

Buccal Film Composition

Mucoadhesive polymers

Correct choice of *mucoadhesive* polymers is crucial step of development of right *mucoadhesive* drug delivery system. These polymers should be quickly adhesive, stable, inert, nonirritant, nontoxic, cost effective and should be compatible with drugs.[39]

Mucoadhesive polymers are of following types:[40,45-48]

Type	Example
Natural	Tragacanth, Sodium alginate, Guar gum, Xanthan gum, Soluble starch, Gelatin, Chitosan, *Lectins (*Lectins are naturally occurring proteins), Antigen K99-fimbriae, an attachment protein derived from E. coli
Synthetic	Polyacrylic acid (PAA), Polyvinyl alcohol (PVA), Sodium carboxymethylcellulose (NACMC), Hydroxypropylmethyl cellulose (HPMC), Hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC) and Sodium alginate, glycerylmonooleate (GMO), Thiolated polymers (thiomers) of polyacrylates, chitosan or deacetylatedgellan gum

Plasticizers[41]

To improve flexibility, flow, and strength and reduce brittleness of *mucoadhesive* films, plasticizers are very helpful. Like polymer, plastisizer

is essential ingredient of the film formulation in the concentration of 0–20% w/w of dry polymer weight. Choice of plasticizers depends on compatibility and type of polymers and solvent solubility. Excess amount or incorrect choice of plasticizers can cause film cracking, splitting and peeling.

Example: Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil

Penetration or permeation enhancers[42,47-48]

Penetration or permeation enhancers are useful to deliver drug smoothly into systemic circulation by interacting mucosal layer. Examples of few penetration enhancers are listed in Table 2. Mode of action of these chemicals is not clear but following hypothesis are made by researchers:

- By reducing viscosity of the mucus and saliva as mucus and saliva are two major barriers
- By raising flexibility of lipid bilayer membrane through disturbing intracellular either lipid or protein packing
- By interacting and disturbing desmosomes which are components at rigid junctions
- By inhibiting peptidases and proteases enzymes within Buccal mucosa and overcoming enzymatic barrier
- By altering the partition coefficient and raising thermodynamic activity of drugs causes change in solubility

Table 2: List of Permeation Enhancer

No.	Permeation Enhancer	No.	Permeation Enhancer
1	1,2- Lauryl Ether	15	Phosphatidylcholine
2	Aprotinin	16	Polyoxyethylene
3	Azone	17	Polysorbate 80
4	Benzalkonium chloride	18	Phosphatidylcholine
5	Cetylpyridinium chloride	19	Sodium EDTA
6	Cetyltrimethyl ammonium	20	Chitosan
7	Bromide	21	Sodium glycocholate
8	Cyclodextrin	22	Sodium glycodeoxycholate
9	Dextran sulfate	23	Sodium lauryl sulfate
10	Glycol	24	Sodium salicylate
11	Lauric acid	25	Sodium taurocholate
12	Lauric acid/Propylene	26	Sodium taurodeoxycholate
13	Lysophosphatidylcholine	27	Sulfoxides
14	Menthol		

Enzyme inhibitors

Presence of number of enzymes is one of the major barrier in drug delivery from oral mucosa but when coad ministration of a drug with enzyme inhibitors or thiol derivatives of polymers is considered then it helps in enhancement of *Buccal* absorption of drugs.

Most of the enzyme inhibitors cause confirmational changes in enzymes by interacting co-factors and thus loss of enzymetic activity is obtained.

Examples: bestatin, puromycin, aprotinin, polyacrylic acid (carbomer) derivatives and chitosan derivatives

Sweetening agents[43]

A compound that gives sweet taste is called as sweetener. Low molecular weight carbohydrate and in particular sucrose are traditionally the most widely used sweetening agent/sweetener. Sucrose has the advantages of being colourless, high water solubility, and stability over wide pH range and imparts pleasant texture, quick, clean and short-lived sweet taste.

Due to these qualities, sucrose is the gold standard for sweet taste. It is important functional ingredient for preparing attractive foods. But metabolism of sucrose and their fermentable products are proven to be causes of diabetes, obesity and even caused tooth decay hence there is strong demand for healthy, natural alternative sweeteners.

Sweeteners are used alone or in combination between 2 to 6%w/w of weight of the film. Alternative sweeteners are classified as follows:

Nutritive sweeteners	Less caloric and sweet than sugar but retain many of the sugars desirable chemical and physical properties, hence mostly used as bulking agent in sugar free products. e.g. sorbitol, mannitol, xylitol, maltitol, lactitol, erytritol, Fructose
Non-nutritive sweeteners	Potently sweet and required in minute quantities. e.g. fruit sugars, aspartame, saccharin, cyclamate, acesulfame, stevieoside, glycyrrhizin
Artificial sweeteners	These are prepared synthetically and most preferred sweeteners. e.g. Aspartame, saccharin, sorbitol, mannitol, acebilfame
Natural sweeteners	These are obtained naturally from plant or animal sources and are of lesser importance. e.g: Plant: Glycyrrhizin, Neohesperidin, Stevioside, Rebaudioside, Thaumtin Animal: Honey, Lactose from cow milk.

Flavoring agents[44]

Preferably, up to 10%w/w flavours are added in the *Buccal* film formulations. Flavour or flavour is the sensory impression of a food or other substance, and is determined mainly by the chemical senses of taste and smell.

Taste modifying compounds have always attracted human being and so researched too. Taste of food is limited to the seven basic tastes i.e. sweet, sour, bitter, salty, spicy, savoury and metallic. There are three principal types of flavourings used in foods:

Natural flavouring substances: Flavouring substances obtained from plant or animal raw materials, by physical, microbiological or enzymatic processes. They can be either used in their natural state or processed for human consumption, but cannot contain any nature-identical or artificial flavouring substances.

Nature-identical flavouring substances: Flavourings substances that are obtained by synthesis or isolated through chemical processes, which are chemically and organoleptically identical to flavoring substances naturally present in products intended for human consumption. They cannot contain any artificial flavoring substances.

Artificial flavoring substances: Flavoring substances not identified in a natural product intended for human consumption, whether or not the product is processed. These are typically produced by fractional distillation and additional chemical manipulation of naturally sourced chemicals, crude oil or coal tar. Although they are chemically different, in sensory characteristics are the same as natural ones.

Example: Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg, vanilla, cocoa, coffee, chocolate and citrus, Apple, raspberry, cherry, pineapple and cooling agents like mono methyl succinate

Colouring agents

Not more than 1%w/w of FD&C approved coloring agents in *Buccal* film is prefred. Example: titanium dioxide

Organoleptic evaluation	Visual inspection of developed film formulation can provide results of desired organoleptic properties like colour, flavour, and taste. E-tongue software are useful to determine taste of formulation. Uniformity in colour and odour along with good taste brings patient acceptability.[49]
Surface pH	pH of film should be near to 7 or neutral to get absorb through oral mucosa without irritation and toxic effects. Film dissolved in suitable solvent is used to determine surface pH-by-pH meter.[50]
Contact angle	Contact angle measurement is useful to predict the wetting property, disintegration and dissolution time of film. Specially designed apparatus attached with digital camera takes the picture of drop of double distilled water placed on the surface of dry film within ten seconds and further analyses using software to determine exact contact angle.[51]
Transparency]	Transparency of oral film measure the transmittance of film using ultraviolet (UV) spectrophotometer as follows: Transparency = (log T600)/b = −€c Where T600 = transmittance at 600 nm, b = film thickness (mm) and c = concentration.[52]
Swelling studies	Swelling studies for *Buccal* films can be determined gravimetrically in phosphate buffer, of pH 6.6. Put films to pre-weighed glass supports using a cyanoacrylate adhesive sealant. Immerse supports with films into the phosphate buffer at 37 °C. Remove the devices at pre- determined time intervals, from the media, blott with tissue paper to remove excess water, and weigh.53 After determination of the wet weight, the films should be dried at 40°C until constant mass. Determine Swelling index (S.I) and erosion gravimetrically according to the following equations. Swelling index (%) =Ws−WdWd Erosion (% mass loss) =Original weight−remaining dry weight/Original weight×100 Where Wd and Ws are the weights of dry and swollen devices, respectively.
Thickness	Film with uniform and optimum thickness in range 5-200 µm can provide accurate dose and good absorption. Measurement of thickness of film either is done by micrometer screw gauge or calibrated digital Vernier Calipers or any other specially designed measurement apparatus. Five different locations i.e four corners and centre should be used to determine thickness.[54]
Interaction study	Drug-excipients interaction study using FTIR spectrum or DSC thermo gram is necessary to develop effective *Buccal* film.[55]
Tensile strength	Maximum stress applied when film specimen breaks is called Tensile strength. It is measure of applied weight at rupture divided by the cross-sectional area of film. Tensile strength = weight at failure × 100/film thickness × film width[52]
Percent elongation	Stretching capacity of film after application of stress up to deformation of film before it gets broken can be expressed in percent elongation capacity. It is calculated by the formula: % Elongation = Increase in length of film × 100/Initial length of film.[53]
Tear resistance	Tear resistance is the measure of maximum resistance offered at low rate up to 50 mm/min by a film before tearing specimen offers when some load or force is applied on the film specimen. A hard and brittle films shows a high tensile strength.[56]
Folding endurance	Folding endurance is the measure of brittleness of a film, which can be measured by repeatedly folding 2 × 2 cm2 film specimen at the same place until it breaks or a visible crack observed.[57]
Percentage moisture loss	To determine physical stability and integrity of the film, percentage moisture loss of films to be determine. Loss in weight of 2 × 2 cm2 film after keeping film in simple desiccators containing fused anhydrous calcium chloride for 72 hr. by using the formula: Percent moisture loss = (Initial weight − Final weight)/Initial weight × 100[58]
Percentage moisture absorption	The *Buccal* films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminum chloride up to 86% relative humidity. After 3 days, the films were taken out and weighed.[59] Percent moisture absorption = (Final weight -Initial weight)/Initial weight × 100
Drug content uniformity	Content uniformity is determined by as per standard assay described for the specific active drug in any of the standard pharmacopoeia. It varies in range of 85-115%.[59]
Scanning electron microscopy	Scanning electron microscopy is very advance technique to understand surface morphology of film and drug - excipients interaction too.[57-59]
***In vitro* disintegration test**	For effective absorption through oral mucosa, film should disintegrate means breaks in contact with water or saliva within 5-30s time.[58-59]
***In vitro* dissolution studies**	Dissolution studies are important to determine the release of active drug into the dissolution medium per unit time at controlled conditions of liquid/solid interface, concentration and 37 ± 0.5°C of temperature and 50 rpm.[55]
Permeation studies	Even though permeability of oral mucosa is 4-1000 times greater than that of skin, permeation studies should be carried out. To study the permeability, modified Franz diffusion cell can be used along with porcine *Buccal* mucosa. The Franz diffusion cell consists of a donor and a receptor compartment. In between the two compartments, mucosa is mounted and the size of the mucosa should be of the same size as that of the head of receptor compartment. The receptor compartment is filled with buffer and maintained at 37 ± 0.2°C and to maintain thermodynamics a magnetic bead stirring at a speed of 50 rpm is used. A film specimen moistened with a few drops of simulated saliva should be kept in contact with mucosal surface. The donor compartment should consist of 1 ml simulated saliva fluid of pH 6.8. At particular interval, samples are withdrawn and replaced by same amount of fresh medium. By suitable analytical method, percentage of drug permeated can be determined.[54]

Stability study in Human saliva	The stability study of films was performed in natural human saliva. Samples of human saliva were collected from 10 humans (ages 18-40 years) and filtered. The films were placed in petriplate containing 5 ml of human saliva and put in a temperature controlled oven at 37°C ± 0.2°C for 6 h. The films were examined for changes in morphology and physical stability at definite time intervals. The prepared formulation was placed in natural human saliva containing petridish and these were checked regularly for the appearance, colour, shape and physical stability. The results were indicate there is no change in the film physical properties hence the prepared formulation is more stable during administration or placed in the Buccal cavity throughout the period.[52,56-59]
Stability study as per ICH guidelines	To determine stability of formulation International Conference on Harmonization (ICH) guidelines are used. Well-packed films should be stored for 3 months at different storage conditions of humidity, temperature and then all possible parameters like drug content, disintegration time, and physical properties should be determined.[57-59]

Characterisation of buccal films

various parameters for characterisation of buccal films is given in the table

CONCLUSION

Thus it can be concluded that *Buccal* drug delivery is most promising drug delivery in *mucoadhesive* system. Range of dosage forms can be incorporated in *Buccal* drug delivery. But *Buccal* films are more popular due to simplicity in preparation, drug loading and characterisation. First pass metabolism prone drugs can be administered by this non-invasive drug delivery system of *Buccal* film.

ACKNOWLEDGEMENT

Nil.

CONFLICT OF INTEREST

Nil.

ABBREVIATIONS USED

cm: Centimeter; **mm:** Milimeter; **ml:** Mililiter; **µm:** Micrometer; **h:** Hour; **ICH:** International Conference on Harmonisation; **GIT:** Gastro-intestinal tract; **% w/w:** Percentage weight by weight.

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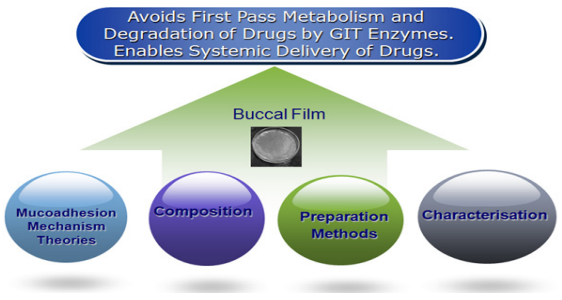
GRAPHICAL ABSTRACT



SUMMARY

- Buccal drug delivery is most promising drug delivery in *mucoadhesive* system.
- Buccal films are more popular due to simplicity in preparation, drug loading and characterisation.
- Buccal films mediated drug delivery bypasses first pass metabolism and offers unique advantages over traditional dosage forms.

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