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AN OVERVIEW ON MUCOADHESIVE BUCCAL PATCHES

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ABSTRACT

Buccal delivery is considered to be a major alternative to the peroral route and the unique environment of the oral cavity offers its potential as a site of drug delivery. Buccal drug delivery has lately become an important route of drug administration. The rich in vascularization of oral mucosa and its permeability too many drugs make this route an attractive alternative to the oral and parenteral routes for systemic drug delivery. Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastrointestinal tract, avoids active drug loss due to presystemic metabolism (First-pass hepatic metabolism), acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved. There is always increase in demand for the patient convenience and compliance related research and novel methods are the development of mucoadhesive buccal formulations which results the greater bioavailability with reducing dose frequency to mouth plasma peak levels, which inturn minimize adverse/side effects and also make it cost effective. In the present review, recent advancements and literature regarding mucoadhesive buccal patches is compiled and it suggests that this delivery system can be adopted by various pharmaceutical companies in the future at the large scale because it is the novel frontier in drug delivery technology that provides a very convenient means of taking medication. There also been significant increases in the number of new chemical entities under development using a mucoadhesive drug delivery technology.
INTRODUCTION
Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. The American Society of Testing and Materials has defined adhesion as the state in which two surfaces are held together by interfacial forces, which may consist of valency forces, interlocking action or both. The transmucosal drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, oral cavity) offers distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass first pass effect, avoidance of presystemic elimination within gastrointestinal tract, and depending on the particular drug, a better enzymatic flora for drug absorption. The potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms could significantly affect drug absorption from this site. Even through rectal, vaginal and ocular mucosae all offer certain advantages the poor potential acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. On other hand, the oral cavity is highly acceptable by patients, the mucosae is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage, and virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. The mucin lining exists in oral mucosa offers an opportunity to develop mucoadhesive system, which retain at absorption site for prolonged time by mucoadhesive binding. The close contact with absorption membrane causes more absorption of the drug and it provides direct entry of drug molecule into the systemic circulation, thus avoiding acid hydrolysis and presystemic metabolism.

The buccal mucosa permits a prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route. Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. The continuous secretion of saliva results in rapid removal of released drug and this may desire that the oral cavity should be restricted to the delivery of the drugs, which have a short systemic circulation. Conversely, the thin mucin film, which exists on the surface of oral mucosa, may provide an opportunity to retain for longer time and continuous drug delivery. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively. The ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. It must
also exhibit good mucoadhesive strength so that it can be retained in mouth for desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated.

Advantages of Buccal Drug Delivery System: The administration of drugs by the buccal route has several main advantages over peroral administration, including the following:

- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is maintained by continuous drug release.
- Drug release in controlled manner for prolonged period.
- Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
- Increased residence time combined with controlled API release may lead to lower administration frequency.
- Tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers.
- It offers a passive system of drug absorption and does not require any activation.
- Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents etc.
- The drug is not subjected to the destructive acidic environment of the stomach.
- The oral mucosa is easily accessible, which ensures that a dosage form can be applied to the required site and removed easily in case of emergency.
- There is no requirement of medical practitioner to administer the dosage form.

The ease of administration and ability to terminate drug delivery when required makes it either a potential route or an attractive for drug delivery.

Disadvantages of Buccal Drug Delivery System: The main challenges of buccal administration are:

- Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm² of which ~50 cm² represents non-keratinized tissues, including buccal membrane.
- The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa.
- Continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
- The hazard of choking by involuntarily swallowing the delivery system is a concern.
Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

OVERVIEW OF THE BUCCAL MUCOSA

The oral mucosa lines the oral cavity, which is delineated by the lips, cheeks, hard and soft palates, tongue and floor of the mouth. It covers a surface area about 100 cm². 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 the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the Pathophysiological state. However, it has the following general composition:

- Water - 95%
- Glycoproteins and Lipids - 0.5 to 5%
- Mineral salts - 0.5 to 1%
- Free Proteins - 0.5 to 1%

The surface of the buccal mucosa consists of stratified squamous epithelium supported by a connective tissue termed lamina propria and separated from the epithelium by basal membrane. Three different types of oral mucosa are recognized:

Masticatory mucosa:

The masticatory mucosa, representing 25% of the total oral mucosa and being 100-200 µm in thickness covers the gingival and the hard palate regions and is tightly attached to the underlying structures. The epithelium of masticatory mucosa in gingival and hard palate regions are keratinized and further subdivided into four layers, namely Keratinized, Granular, Prickle-cell and Basal layers.

Lining mucosa:

The lining mucosa has a thickness of 500-800 µm and covers the lips, cheeks, soft palate, the lower surface of the tongue on the floor of the oral cavity, representing 60% of total oral mucosa. This lining provides elastic and deformable surfaces that stretch with the normal functions of the mouth, such as mastication and speech. It is attached by a loose and elastic connective tissue to the underlying structures.

Specialized mucosa:

Specialized mucosa accounts for 15% of total oral mucosa and consists of both keratinized and non-keratinized mucosa. It is found on the dorsam of the tongue and is involved in taste.
BUCCAL MUCOSA AS A SITE FOR DRUG DELIVERY

Two sites within the buccal cavity have been used for drug administration to get the systemic effect, Buccal and Sublingual. The buccal delivery allows prolonged localised therapy that enhanced systemic delivery where as the sublingual route is usually used when a rapid onset of action is required.

The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of the routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatine capsules filled with liquid drug. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral transmucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic transmucosal drug delivery\textsuperscript{14}.

First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery. Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well.

One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa\textsuperscript{15}. 
BUCCAL ROUTES OF DRUG ABSORPTION

The mechanisms by which the drugs cross biologic lipid membranes are passive diffusion, active transport, and pinocytosis. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion, although facilitated diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of low concentration within the buccal tissues. Further diffusion then takes into the venous capillary system, with the drug eventually reaching the systemic circulation via jugular vein. There are two permeation pathways for passive drug transport across the oral mucosa: paracellular (intercellular) and transcellular (intracellular) routes. 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 low partition coefficient. Therefore, the intercellular spaces pose as the major 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. Compounds with partition coefficient in the range 40-20000 and pKa 2-10 are considered optimal to be absorbed through buccal mucosa. However the administration site is also a factor. Large size patches can be
administrated at the central position of the buccal mucosa (center of cheek), whereas the sublingual and gingival sites require a rather small sized patches\cite{17,18}. The size of systems typically varies from 1-16 cm, depending upon the specific purpose of the application. Usually, 1-3 cm patches are commonly used because of patient convenience and comfort\cite{19-21}.

**Characteristics of an Ideal Buccoadhesive System**\cite{5}: An ideal buccal adhesive system should possess the following characteristics:
1. Quick adherence to the buccal mucosa and sufficient mechanical strength.
2. Drug release in a controlled fashion.
3. Facilitates the rate and extent of drug absorption.
4. Should have good patient compliance.
5. Should not hinder normal functions such as talking, eating and drinking.
6. Should accomplish unidirectional release of drug towards the mucosa.
7. Should not aid in development of secondary infections such as dental caries.
8. Possess a wide margin of safety both locally and systemically.
9. Should have good resistance to the flushing action of saliva.

**GENERAL COMPOSITION**

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>HPMC</th>
<th>HPC</th>
<th>HEC</th>
<th>PVP</th>
<th>PVA</th>
<th>Carbopol 934P</th>
<th>Eudragit</th>
<th>Chitosan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluents</td>
<td>Lactose CD,MCC, Starch, DCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweetening agent</td>
<td>Aspartame</td>
<td>23</td>
<td>Dextrose</td>
<td>43</td>
<td>Saccarin sodium</td>
<td>39</td>
<td>Mannitol, Sucralose, etc.,</td>
<td></td>
</tr>
<tr>
<td>Flavouring agent</td>
<td>Menthol, Vanillin, Clove oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Backing membrane</td>
<td>Ethyl cellulose</td>
<td>1,25,28,32,33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetration enhancers</td>
<td>Propylene glycol</td>
<td>1,3,22-25,32,35,41,44</td>
<td>Thiolated polymers</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasticizers</td>
<td>Propylene glycol</td>
<td>1,3,22-25,32,35,41,44</td>
<td>Glycerin</td>
<td>25-28,30,31,36,39,42</td>
<td>Castor oil</td>
<td>28</td>
<td>PEG</td>
<td>4</td>
</tr>
</tbody>
</table>
Active pharmaceutical agents:
The active substance is may be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa respectively. According to literature, API can be added from 5%-25% w/w of total weight of polymer. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). The drugs which show high first-pass metabolism and patient non-compliant are best candidates for mucoadhesive buccal patches.

Researchers have shown interest in development of fast dissolving films for drugs like: Antihypertensive, hypoglycaemic, NSAIDs, antiulser agents, antiseptic, antibacterial, antifungal, antimicrobial, topical corticosteroids, local anesthetics, antibiotics and anti-dentalcaries drugs.

Among which preferred active agents include carvedilol, losartan potassium, glipizide, glibenclamide, lornoxicam, aceclofenac, diclofenac, ketorolac, clotrimazole, micanazole nitrate, triamcinolone acetonide, cetylpyridinium chloride, ranitidine, famotidine etc.,

Mucoadhesive polymers:
Mucoadhesive polymers are used to immobilize a drug delivery device on a specific site for targeted release and optimal drug delivery due to intimacy and duration of contact. Mucoadhesive polymers have been developed for buccal, nasal, ocular, vaginal and oral applications.

IDEAL CHARACTERISTICS OF BUCCAL ADHESIVE POLYMERS:
1) Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
2) Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
3) Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
4) Should possess peel, tensile and shear strengths at the bioadhesive range.
5) Polymer must be easily available and its cost should not be high.
6) Should show bioadhesive properties in both dry and liquid state.
7) Should demonstrate local enzyme inhibition and penetration enhancement properties.
8) Should demonstrate acceptable shelf life.
9) Should have optimum molecular weight.
10) Should possess adhesively active groups.
11) Should have required spatial conformation.
12) Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
13) Should not aid in development of secondary infections such as dental caries.

**NEW GENERATION OF MUCOADHESIVE POLYMERS**:47

The new generation of mucoadhesives (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. We have chosen to focus on recently discovered bioadhesive polymers in this review. Examples of such are the incorporation of l-cysteine into thiolated polymers and the target-specific, lectin mediated adhesive polymers. These classes of polymers hold promise for the delivery of a wide variety of new drug molecules, particularly macromolecules, and create new possibilities for more specific drug– receptor interactions and improved targeted drug delivery. Through a covalent attachment between a cysteine (Cys) residue and a polymer of choice, such as polyacrybophi48, polyacrylic acid49 and chitosan50 a new generation of mucoadhesive polymers have been created.

**Improved mucoadhesive properties of the thiolated polymers**: 

1) Improved tensile strength,
2) High cohesive properties,
3) Rapid swelling and water uptake behavior have made them an attractive new generation of bioadhesive polymers.

**Mucoadhesive polymers used in the oral cavity**:47,51:

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

**Permeation enhancers:**

As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers plays a key role in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of vehicle and other excipients. In some cases the usage of enhancers in combination has shown synergistic effect than the individual enhancers. Because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions the efficacy of an enhancer in one site is not the same in the other site.

Most of the compounds are predominantly oil soluble, whereas others are charged surfactants that can readily interact with oppositely charged molecule, thereby limiting their compatibility with many drugs and excipients.
List of compounds used as oral mucosal permeation enhancers\textsuperscript{11,47,52}:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bile salts</td>
<td>Sodium glycocholate, Sodium taurocholate, Sodium deoxycholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate</td>
</tr>
<tr>
<td>2</td>
<td>Fatty acids</td>
<td>Oleic acid\textsuperscript{53}, Methyloleate\textsuperscript{53}, Capric acid, Lysophosphatidylcholine\textsuperscript{54}, propylene glycol\textsuperscript{55}, Phosphatidylcholine\textsuperscript{55}, Lauric acid\textsuperscript{55}, Caprylic acid</td>
</tr>
<tr>
<td>3</td>
<td>Surfactants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Non-ionic Surfactants</td>
<td>Laureth-9, Polysorbate 80, Dodecylmaltoside, Sucrose esters</td>
</tr>
<tr>
<td></td>
<td>b. Cationic Surfactants</td>
<td>Cetylpyridiniumchloride\textsuperscript{60,61}, Cetyltrimethylamm. bromide\textsuperscript{62}</td>
</tr>
<tr>
<td></td>
<td>c. Anionic Surfactants</td>
<td>Sodium glycodeoxycholate, Sodium lauryl sulfate\textsuperscript{55}, Sodium glycocholate\textsuperscript{56}</td>
</tr>
<tr>
<td>4</td>
<td>Chelators</td>
<td>Ethylene diamine tetra acetic acid (EDTA)\textsuperscript{57}, Sodium salicylate and Methoxysaliylates\textsuperscript{63,64}</td>
</tr>
<tr>
<td>5</td>
<td>Others</td>
<td>Sulfoxides\textsuperscript{55}, Aprotinin\textsuperscript{57}, Azone\textsuperscript{56-59}, Menthol\textsuperscript{64}, Cyclodextrin\textsuperscript{61}, Dextran sulfate\textsuperscript{63}, Phospholipases, Neuraminidase and Chondroitinase ABC, Unsaturated cyclic ureas and Cyclodextrins.</td>
</tr>
<tr>
<td>6</td>
<td>Thiolated polymers</td>
<td>Chitosan-4-thiobutylamide, Chitosan-cysteine, Polycarbophil-cysteine, Polycarbophil-cystein\textsuperscript{48}, Poly(acrylic acid)\textsuperscript{49}, Chitosan-4-thioglycolic acid\textsuperscript{50}</td>
</tr>
</tbody>
</table>

**Plasticizers:**

Plasticizer is a vital ingredient of the buccal films formulation. The mechanical properties such as tensile strength and elongation to the films can be improved by the addition of the plasticizer. It also helps to improve the flexibility of the strip and reduces the brittleness of the strip. They also improve the strip properties by reducing glass transition temperature of the polymer. The flow of polymer also gets better by the addition of the plasticizer. Variations in their concentration affect these properties. The selection of the plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in its casting. Plasticizers include glycerine, sorbitol, propylene glycol, polyethylene glycol, triacetin, di- butylphthalate, triethyl citrate, acetyl triethyl citrate and other citrate esters. Typically the plasticizers are used in the concentration of 0-20% w/w of the dry polymer weight. Inappropriate use of the plasticizer may lead to film cracking, splitting, peeling of the strip and it may also affect the absorption rate of the drug\textsuperscript{65}.  

Full Text Available On www.ijupls.com
Flavoring agents:
Flavoring agents can be selected from the synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Any flavor can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweetmint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary flavors such as vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

Coloring agents:
A full range of colours is available including FD&C colors, EU colours, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc dioxide and custom pantone-matched colours. These all coloring agents should not exceed concentration levels of 1% w/w. these agents are incorporated when some of the formulation ingredients or drugs are present in insoluble or suspension form.

METHOD OF MANUFACTURING
Two methods used to prepare adhesive patches include,

Solvent casting
In this, all patch excipients including the drug codispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation, a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used. These drawbacks can be overcome by the hot-melt extrusion method.

Water soluble ingredients are dissolved in H₂O and API and other agents are dissolved in suitable solvent to form a clear viscous solution

Both the solutions are mixed

Resulting solution is cast as a film and allowed to dry

Film is collected
Direct milling
In this, patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved.
An impermeable backing membrane may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during application period.

API and excipients are blended by direct milling

Blended mixture is rolled using rollers

Backing material is laminated

Film is collected

While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

CHARACTERIZATION

Drug-excipients interaction studies:
Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra-Red Spectrum (FTIR), Differential scanning calorimeter(DSC), thin layer chromatography and X Ray Diffraction (XRD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction.

Physical evaluation
It includes- Weight uniformity, Content uniformity, and Thickness- uniformity. Weigh variation was tested by comparing the averages weighed of 10 different randomly selected patches from each batch with individual patch. The thickness of the film sample should be measured at five locations (centre and four corners), and the mean thickness is calculated. Samples with air bubbles, nicks or tears and having mean thickness variation of greater than
5% are excluded from analysis. Three patches (each of 20mm diameter) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analysed by using UV spectrophotometer. The average of three patches was taken as final reading.

**Surface pH**

The surface pH of the buccal patch was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and pH was note down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute.

**Swelling studies:** Weight and area increase due to swelling were measured

*Weight increase due to swelling:* A drug-loaded patch of 1x1 cm² was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every five minutes, the cover slip was removed and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

*Area increase due to swelling:* A drug loaded patch size of 1x1 cm² was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, %S, was calculated using the following equation:

\[
\%S = \frac{X_t - X_o}{X_o} \times 100
\]

Where \(X_t\) is the weight or area of the swollen patch after time \(t\)

\(X_o\) is the original patch weight or area at zero time.

**Palatability test:**

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A
grade then it would be considered as good and the one with all three A grade it would be the very good formulation\textsuperscript{67}. Grades: A = very good, B = good, C = poor.

**Ex vivo mucoadhesive strength**

A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 37\textdegree{}C. The buccal mucosa cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two sides of the balance made equal before the study, by keeping a 5 g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time\textsuperscript{26}. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37\textdegree{}C ±1\textdegree{}C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive\textsuperscript{72}.

**Ex vivo mucoadhesive time**

The ex vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8, and kept at 37\textdegree{}C ± 1\textdegree{}C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the buccal mucosa was recorded as the mucoadhesion time\textsuperscript{65}.

**In vitro drug release**

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug release from the bilayered and multilayered tablets. The dissolution medium consisted of phosphate buffer pH 6.8. The release was performed at 37\textdegree{}C ± 0.5\textdegree{}C, with a rotation speed of 50 rpm. The backing layer of buccal tablet attached to the glass disk with instant adhesive
(cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm.

**In vitro drug permeation**

The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A one ml sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UV-spectrophotometer.\(^{73}\)

**Stability study in Human saliva**

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance.\(^{65}\)

The stability study of optimized mucoadhesive patch formulation was performed at 40°C, 37 ±5°C & 75±5% RH for three months. The value of all parameter after three months remain same as their values and minor changes occur in value of volume entrapment efficiency, % elongation & % drug release after 8 hour which was considerable.\(^{37}\)

**Measurement of mechanical properties**

Mechanical properties of the patches were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Film strip with the dimensions 60 x 10 mm and without any visual defects were cut and positioned between two clamps separated by a distance of 3 cm. Clamps were designed secure the patch without crushing it during the test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and elongation at break values were calculated using the formula.\(^{74}\)
Force at break (kg)

\[
\text{Tensile strength (kg. mm}^{-2} = \frac{\text{Initial cross sectional area of the sample (mm}^2)}{\text{Increase in length (mm)}}
\]

Elongation at break (%.mm^{-2}) = \frac{\text{Increase in length (mm)}}{\text{Original length} \times \text{Cross sectional area (mm}^2)} \times 100

**Folding endurance**

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on five patches.

**Viscosity**

Aqueous solutions containing both polymer and plasticizer prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number 4 used. The viscosity measured at 20 rpm at room temperature. The recorded values the mean of three determinations^{17,75,76}.

**Ageing**

Patches subjected to accelerated stability testing. Patches packed in glass Petri dishes lined with aluminium foil and kept in an incubator maintained at 37±0.5°C and 75±5%RH for 6 months. Changes in the appearance, residence time, release behaviour and drug content of the stored bioadhesive patches investigated after 1, 2, 3, 4, 5, and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, investigated using scanning electron microscope^{65}.

**Packing**

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three films on each side. Every dose can be taken out individually. The material selected must have the following characteristics:
✓ They must protect the preparation from environmental conditions.
✓ They must be FDA approved.
✓ They must meet applicable tamper-resistant requirement.
✓ They must be non-toxic.
✓ They must not be reactive with the product.
✓ They must not impart to the product tastes or odors.

FUTURE TRENDS
Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa.

The future challenge in the development of buccoadhesive dosage forms is to modify the permeability barrier of the mucosa using safe and effective penetration enhancers. Mucoadhesive drug delivery systems available in the market include aftach tablet (Triamcinolone acetonide), suradrintablet (Nitroglycerin), Buccostem tablet (prochlorperazine maleate), Salcoat powder sprays (Beclomethazone-dipropionate), Rhinocort powder spray (Beclomethazone Dipropionate) and sucralfate (Aluminum hydroxide). Though 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. Various strategies are being employed to achieve oral absorption of peptides. These strategies include manipulation of the formulation (e.g. inclusion of penetration enhancers or protease inhibitors etc.), maximizing retention of the delivery system at the site of absorption, and alteration of the peptide so as to optimize affinity for endogenous transport systems, build in chemical and metabolic stability, minimize the size and optimize the balance between lipophilicity and hydrogen bonding potential.

CONCLUSION
Buccal adhesive systems offering numerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. This overview about the mucoadhesive buccal patches might be useful tool for
the efficient design and characterization of mucoadhesive buccal patches. Mucoadhesive buccal patches have applications from different angles includes avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability in the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

**LIST OF INVESTIGATED BUCCAL MUCOADHESIVE PATCHES**

<table>
<thead>
<tr>
<th>Active pharmaceutical ingredient</th>
<th>Reference</th>
<th>Active pharmaceutical ingredient</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>37</td>
<td>Metoprolol tartrate</td>
<td>41,85</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>21,77,78</td>
<td>Miconazole nitrate</td>
<td>22,86</td>
</tr>
<tr>
<td>Atenolol</td>
<td>79</td>
<td>Montelukast sodium</td>
<td>87</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>80,81</td>
<td>Oxytocin</td>
<td>88,89</td>
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<tr>
<td>Carvedilol</td>
<td>25,30,42</td>
<td>Pimozide</td>
<td>31</td>
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<tr>
<td>Cetylpyridinium chloride</td>
<td>36</td>
<td>Prochlorperazine</td>
<td>74</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>24,35</td>
<td>Propranolol hydrochloride</td>
<td>70,90</td>
</tr>
<tr>
<td>Diltiazem Hydrochloride</td>
<td>28</td>
<td>Protirelin</td>
<td>91,96</td>
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<tr>
<td>Insulin</td>
<td>82</td>
<td>Salbutamol sulphate</td>
<td>4,92</td>
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<td>Lignocaine</td>
<td>83</td>
<td>Sumatriptan succinate</td>
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<tr>
<td>Lornoxicam</td>
<td>23,40</td>
<td>Terbutalinesulphate</td>
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<td>Losartan Potassium</td>
<td>2</td>
<td>Thyrotropin-releasing hormone</td>
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<tr>
<td>Melatonin</td>
<td>84</td>
<td>Verapamil Hcl</td>
<td>38</td>
</tr>
</tbody>
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