DRUG DELIVERY VIA THE BUCCAL PATCH – A NOVEL APPROACH
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ABSTRACT

The successful delivery of drugs across the oral mucosa represents a continuing challenge, as well as a great opportunity. Buccal delivery has progressed far beyond the use of traditional dosage forms with novel approaches emerging continuously. Buccal drug delivery system in which drug enters directly in systemic circulation thereby by passing the first pass effect. Contact with digestive food of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers. The buccal route has been researched for a wide variety of drugs like miconazole nitrate, Aceclofenac, Cyproheptadine Hydrochloride and various different categories and has gained significant attention and momentum since it offers remarkable advantages. Over past few decades, buccal route for systemic drug delivery using mucoadhesive polymers to significantly improve the performance of many drugs has been of profound interest. Many ways of research work may be carried out to develop more this formulation for delivery of drug.

Keywords:
Buccal Patch, Mucoadhesion, Polymers, Evaluation of Patch.

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INTRODUCTION

Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity). Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as a mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.1,2

Components or structural features of oral cavity 2,3

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions. Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate.

The tongue projects from the floor of the cavity.

Buccal Drug Delivery

Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Substantial efforts have recently been focused on placing a drug or drug delivery system in a particular region of the body for extended periods of time. The mucosal layer lines a number of regions of the body including the oral cavity, gastrointestinal tract, the urogenital tract, the airways, the ear, nose and eye. Hence the mucoadhesive drug delivery system can be
classified according to its potential site of applications. The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Based on current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically produced drugs, they cannot be delivered effectively through the conventional oral route. Because after oral administration many drugs are subjected to pre-systemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability. Direct access to the systemic circulation through the external jugular vein by pass the drugs from the hepatic first pass metabolism which may lead to higher bioavailability.4,5

**Advantages of Buccal Drug Delivery System**5-9

- Excellent accessibility
- Presence of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms
- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability
- Low enzymatic activity
- Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa
- Painless administration
- Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.
- Oral mucosal drug delivery systems are easy and painless to administer and well accepted by the patient.
- Precise dosage form localization is possible and there is ability to terminate delivery when required.
- Flexibility in physical state, shape, size and surface.
- For patient suffering with nausea or vomiting or in the state of unconsciousness, with an upper gastrointestinal tract disease or surgery which affects oral drug absorption, the oral cavity a useful site for drug delivery for upper symptoms.
- Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.
- Excellent route for the systemic delivery of drug with high first pass metabolism, thereby offering a greater bioavailability.
- A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
- Drugs which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestines can be administered by this route.
- It offers a passive system for drug absorption and does not require any activation.
- It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
- The oral mucosa lacks prominent mucus secreting goblets cells and therefore there is no problem of diffusion limited mucus buildup beneath the applied dosage form.
The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.

- It satisfied several features of the controlled release system.
- It can be made unidirectional to ensure only buccal absorption.
- Bioadhesion prolongs the residence time at the site of drug absorption, and thus improves bioavailability and dosing interval.
- Rapid onset of action.

**Limitation**

Drug administration via this route has certain limitations

- Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.

**Ideal Drug Candidates for Buccal Drug Delivery System**

1. Molecular size – 75-600 Daltons
2. Molecular weight between 200-500 Daltons.
3. Drug should be lipophilic or hydrophilic in nature.
4. Stable at buccal pH.
5. Taste – bland
6. Drug should be odourless.
7. Drugs which are absorbed only by passive diffusion should be used.

**Design of Buccal Dosage Form**

**Matrix Type**

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

**Reservoir Type**

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. Impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

**Factors Important to Mucoadhesion**

**Polymer Related Factors**

1. *Molecular weight*: In certain molecular weight at which bioadhesion is at a maximum. The interpenetration of polymer molecule is favorable for low molecular weight polymer whereas entanglements are favoured for high molecular weight polymers. The optimum molecular weight for maximum bioadhesion depends upon the type of polymers. According to Gurny et al. (1984) it seems that the bioadhesive force increased with the molecular weight of the bioadhesive polymers upto 100,000 and beyond this level there is not much effect. But size and configuration of the polymers
molecule are also important factors e.g. polyethylene oxide adhesive strength increases even up to molecular weight of 4,000,000. These molecules are of highly linear configuration.

2. Concentration of active polymer: Bremecker (1983) maintains that there is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated system, the adhesive strength drops significantly.

3. Flexibility of Polymer Chains: It is important for interpenetration and enlargement. As water-soluble polymers become cross-linked, the mobility of the individual polymer chain decreases. As the cross-linking density increases, the effective length of the chain which can penetrate into the mucus layer decreases even further and mucoadhesive strength is reduced.

4. Spatial conformation: Spatial conformation of molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to that of polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesive active groups. Primarily responsible for adhesion unlike PEG polymers which have a linear conformation.

Environment Related Factors-

1. Applied Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength the adhesion strength increased with the applied strength or with the duration of its application up to an optimum. If high pressure is applied for longer period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

2. Initial contact time: The mucoadhesive strength increased as the initial contact time increases.

3. Selection of the model substrate surface: It should be necessary for examining the properties like permeability, electrophysiology or histology.

4. Swelling: Swelling depends both on polymer concentration and on presence of water. When swelling is too great, a decrease in bioadhesion occurs.

Physiological Variables

1. Mucin turnover: It is important for two reasons.
   a. The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. Mucoadhesives are detached from the surface due to mucin turnover.
   b. Mucin turnover result in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesive before they have a chance to interact with mucus layer.

2. Disease states: The physiochemical properties of the mucus are known to change during disease condition such as common cold, gastric ulcers, ulcerative colitis etc.

Methods to Increase Drug Delivery via Buccal Route

Penetration enhancers

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inters/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate.
<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactants</td>
<td>Anionic: Sodium lauryl sulfate, Cetyl pyridinium chloride, Nonionic: Poloxamer, Brij, Span, Myrij, Tween</td>
<td>Perturbation of intercellular Lipids and protein domain integrity</td>
</tr>
<tr>
<td>Bile salts</td>
<td>Sodium glycol deoxycholate, Sodium glycocholate, Sodium tauro deoxycholate, Sodium tauro cholate</td>
<td>Perturbation of intercellular Lipids and protein domain integrity</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Oleic acid, Caprylic acid, Lauric acid, Lyso phosphatidyl choline, Phosphatidyl choline</td>
<td>Increase fluidity of phospholipid domains</td>
</tr>
<tr>
<td>Cyclodextrins</td>
<td>α, β, γ, Cyclodextrin, methylated β-cyclodextrins</td>
<td>Inclusion of membrane Compounds</td>
</tr>
<tr>
<td>Chelators</td>
<td>EDTA, Citric acid, Sodium salicylate, Methoxy salicylates</td>
<td>Interfere with Ca+</td>
</tr>
<tr>
<td>Positively charged Polymers</td>
<td>Chitosan, Trimethyl chitosan</td>
<td>Ionic interaction with negative charge on the mucosal surface</td>
</tr>
<tr>
<td>Cationic Compounds</td>
<td>Poly-L-arginine, L-lysine</td>
<td>Ionic interaction with negative charge on the mucosal surface</td>
</tr>
</tbody>
</table>

**Work Done in the Field of Buccal Patch**

Probably, the first oral adhesives used in the mouth were developed in dental practice, in the last 1950's. One example is the "orohesive bandage" prepared to gelatin, sodium CMC & poly isobutylene backed by a layer of polyethylene film on one side and a layer of removable paper on the other. The research in Bioadhesion was continued in 1970 by Chen & Crys.

In the early 1980's the systemic investigations on mucoadhesive begin and a lot of excellent work has been done on the development of mucoadhesive buccal drug delivery system both for systemic and local use. Various devices in the form of single and multilayered tablets, laminated patches, adhesive films, ointments and gels has been developed using various bioadhesive polymers. However, the method of formulation used and described has mainly been on a laboratory scale.

Sam T Mathew et al (2012) have formulated Mucoadhesive buccal patches of Aceclofenac using different polymers like hydroxypropyl methylcellulose, Carbopol 934-P, polyvinyl alcohol, polyvinyl pyrrolidone K-30. All the formulation showed folding endurance of _100. The prepared patches were smooth, elegant in appearance, uniform in thickness, mass and drug content. The stability studies of selected patches were done in natural human saliva and it was found that all the patches were stable in human saliva.

S. Himabindu et al (2012) designed and evaluated mucoadhesive buccal patches of Cyproheptadine Hydrochloride (CPH) which is a sedating antihistamine with antimuscarinic, serotonin-antagonist, and calcium-
channel blocking action. Buccal films were made with Hydroxy propylcellulose (HPC EF) and Hydroxy Propyl Methyl Cellulose (HPMC E15) as mucoadhesive polymers. The formulation F8 of HPMC E15 was found to give the better results and release of drug from the film followed Higuchi and Korsmeyer and Peppas models.

G. Shaji et al (2011) designed and optimized an oral controlled release Nebivolol mucoadhesive tablet by using HPMC K4M, HPMC K15M and Carbomer-940 as mucoadhesive polymers, which significantly influence characteristics like swelling index, ex-vivo mucoadhesive strength and in-vitro drug release. The results indicate that suitable mucoadhesive buccal tablet with desired property can be prepared.

Bazigha K Abdul Rasool et al (2010) have prepared Five different film formulations containing 20 mg of miconazole nitrate, drug solubilizers (propylene glycol 10% w/w, polyethylene glycol 3% w/w, tween20 6% w/w, and oleic acid 5% w/w) and chitosan as film forming polymer, had been prepared. These preliminary results indicate that the selected film formulation (MC 0.524 mg/cm2, PG 10% w/w and chitosan 2% w/w) can represent a valid mean for the management of oral candidiasis.

Dheeraj Baviskar et al (2009) have prepared Mucoadhesive buccal patch of Aceclofenac using polymer like Gelatin, Poly Sodium CMC and Poly Vinyl Alcohol. Eight formulations were prepared with varying the concentration of Poly Sodium CMC and evaluated for various parameters like weight variation, patch thickness, volume entrapment efficiency %, and measurement of % elongation at break, folding endurance, in vitro mucoadhesive time, in vitro release and stability study.

R. Manivannan et al (2008) Mucoadhesive buccal tablets of Diltiazem hydrochloride were prepared using carbopol-934, Sodium carboxy methyl cellulose (SCMC), Hydroxy propyl methyl cellulose (HPMC), sodium alginate and guar-gum as mucoadhesive polymers. Eight formulations were developed with varying concentrations of polymers. FTIR studies show no evidence on interaction between drug and polymers. Formulation FA2 showed maximum release of 76.98% in 8hours

Bhupendra G. Prajapati et al (2007) prepared the buccal adhesive tablets musing sodium carboxymethylcellulose (SCMC) and Carbopol-934 (CP) as bioadhesive polymers to impart mucoadhesion and ethyl cellulose (EC) to act as an impermeable backing layer. Buccal devices were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, ex vivo mucoadhesion time, in vitro drug release, and in vitro drug permeation. As compared with bilayered tablets, multilayered tablets showed slow release rate of drug with improved ex vivo bioadhesive strength and enhanced ex vivo mucoadhesion time.

A.P. Munasur et al (2006) designed a Box–Behnken experimental to optimise a polymeric blend for the preparation of propranolol HCl matrices with maximum mucoadhesivity and were thereafter modified for achieving controlled drug release. The quantitative effects of the polymers used i.e. poly (acrylic acid) (PAA) and poly(vinyl pyrrolidone) (PVP) on mucoadhesion could be predicted using polynomial equations. A formulation of 20% PAA, 20% CMC and 20% PVP was identified for maximizing mucoadhesivity and obtaining a controlled drug release profile.

Lobna Mohamed Mortada et al (2003) Mucoadhesive patches for delivery of cetylpyridinium chloride (CPC) were prepared using polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and chitosan. Swelling and
bioadhesive characteristics were determined for both plain and medicated patches. The results showed a remarkable increase in radial swelling (SD) after addition of the water-soluble drug (CPC) to the plain formulae. A decrease in the residence time was observed for PVA and chitosan-containing formulae. Higher drug release was obtained from PVA patches compared to HEC ones, while both are non-ionic polymers.

K. Balamlfugam, J.K. Pandit 2001, was developed a systemic absorption of Propranolol hydrochloride delivered through rabbit mucosa was studied from buccoadhesive films by using polymers combination sodium CMC and carbopol with different ratio. S1 & S6 formulation, means alone SCMC (3) and SCMC (2.5) : CP (0.5) having maximum inhibition of the heart rate for longer period of time.

Khurana R. et al. 2000, developed and evaluated mucoadhesive films of Miconazole nitrate for the treatment of oral candidiasis. A film was prepared by casting procedure using various polymer combinations and was evaluated for their in-vitro bioadhesive performance and release characteristics. The formulations containing carbopol-934P and HPMC-M combination was found to give best result.

Shakoor O. et al. 1999 formulated bioadhesive buccal tablets for Nicotine replacement therapy and demonstrated the ability to produce zero-order release from buccal adhesive tablets.

C. Li, P. Bhatt, 1998, has done evaluation of mucoadhesive buccal patch for delivery of peptides; in-vitro screening of Bioadhesion

Khanna et al., 1997 designed muco-adhesive buccal films of clotrimazole using different polymers and propylene glycol. The film was evaluated on the basis of their physical characteristics. A combination of Carbopol-934P and HPMC in the ratio of 1: 5 and using ethanol as the solvent was found to give satisfactory results

`Taylan B. et al. 1996, designed and evaluated sustained release buccoadhesive Propranol hydrochloride tablets using HPMC, carbopol as polymers and 1% magnesium stearate was used as a lubricant. The result of this study demonstrate that buccal adhesive propranol hydrochloride tablets containing PAA: HPMC of 2 : 8 showed suitable release and adhesive properties to the buccal mucus membrane.

Miyazaki S. et al. 1995, prepared bioadhesive tablets of Diltiazem by directly compressing the drug with a mixture of chitosan and sodium alginate. They found that the maximum force of adhesion of these tablet to the membrane increased with increasing alginate content of tablets. They also found that the release from tablets composition of 1 : 4 and 1 : 1 chitosan/ Alginate was rapid with almost 100% release within 3 hrs.

Guo J.H. et al. 1994, prepared bioadhesive buccal patches for Buprenorphine controlled delivery using carbopol 934, HPMC and chitosan and evaluated the in-vitro adhesion and release properties. They found bioadhesive strength of buccal patches increases with increasing thickness up to a maximum value and swelling is the major mechanism of buprenorphine release from buccal patches.

Cassidy et al. 1993, has done the in-vitro study of Buprenorphine to determine its buccal flux. Smart J.D. 1992, evaluated the rate of release of a model water soluble drug from various polyacrylic acid containing
matrices. It was shown that a formulation containing carbopol-934P cross linked with calcium chloride was found to give the slowest rate of drug release (t50% of 7.74) with release kinetics nearest to the ideal zero order.

Bottenberg P. et al. 1991, investigated bioadhesive characteristics of tablet made from modified starch, polyacrylic acid (PAA), PEG and sodium CMC. They observed that despite its long adhesion time in-vivo, clinical application of PAA in the oral cavity is not recommended but when PAA used in small amount together in a non-irritating polymer, PAA improves the bioadhesive qualities of the formulation.

Collins A.E. and Deasy P.B. 1990, studied the release of cetyl pyridinium chloride from two-three layered bioadhesive flavoured device in six healthy human volunteers. It was observed that in comparison with a proprietary lozenge, the device produced more uniform and effective level of drug (20mg/ml), with adequate comfort, taste and non-irritancy over a period of 3 hrs.

Anders R. and Merkle H.P. 1989, developed and evaluated laminated mucoadhesive patches of Protirelin for buccal drug delivery. The patches consisted of the two-ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The duration of mucosal adhesion in-vivo was found to be dependent on the type of polymer used, its viscosity grade, the polymer load per patch and drying procedure for the preparation.

Khar R.K. et al. 1988, developed buccoadhesive erodible films of Triamcinolone acetonide for the treatment of oral lesions using carbopol 934P, hydroxy propyl cellulose-M, HPMC-EUM, HPMC alone and in different ratio. Propylene glycol was used as plasticizer and films were prepared by solvent casting method. They found results obtained from erodible patches of different formulations were comparable.

Yotsuyangi et al. 1985, designed a mucoadhesive, moderately water-soluble polymeric film containing Analgesics and Antibiotics for the treatment of lesions and also to ease the accompanying pain. The film consisted of HPC-M and contained tetracaine, thiamphenicol and triacetin.

Bremecker K.D. et al. 1984, formulated a novel mucosal adhesive ointment based partly on neutralized polymethacrylic acid methyl ester. The rheological behavior as well as the adhesion on the mucosal membrane could be varied by the type and concentration of the polymer used and the base used for neutralization. Both vehicle and preparation were found to be pleasant for patients use.
## Commercially Available Buccal Adhesive Formulations:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Brand Name</th>
<th>Dosage forms</th>
<th>Polymers used</th>
<th>Company</th>
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<tbody>
<tr>
<td>1</td>
<td>Buccastem</td>
<td>Tablet</td>
<td>PVP, Xanthum gum, Locust bean gum</td>
<td>Rickitt Benckiser</td>
</tr>
<tr>
<td>2</td>
<td>Suscard</td>
<td>Tablet</td>
<td>HPMC</td>
<td>Forest</td>
</tr>
<tr>
<td>3</td>
<td>Gaviscon Liquid</td>
<td>Oral liquid</td>
<td>Sodium alginate</td>
<td>Rickitt Benckiser</td>
</tr>
<tr>
<td>4</td>
<td>Orabase</td>
<td>Oral gel</td>
<td>Pectin, gelatin</td>
<td>Orabase</td>
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<tr>
<td>5</td>
<td>Corcodyl gel</td>
<td>Oromucosal Gel</td>
<td>HPMC</td>
<td>Glaxo smithkline</td>
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<tr>
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<td>Corlan pellets</td>
<td>Oromucosal Pellets</td>
<td>Acacia</td>
<td>Celltech</td>
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<td>7</td>
<td>Fentanyl Oralet tm</td>
<td>Lozenge</td>
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<td>8</td>
<td>Miconazole Lauriad</td>
<td>Tablet</td>
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<td>Bioalliance</td>
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<td>9</td>
<td>Emezine TM</td>
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<td>BDSI’s</td>
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<td>BEMA Fentanyl</td>
<td>tablet</td>
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<td>BDSI’s</td>
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<td>Straint Fentanyl</td>
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<td>Zilactin</td>
<td>Buccal film</td>
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<td>Luborant</td>
<td>Artificial Saliva</td>
<td>Sodium cmc</td>
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<td>Wyvem</td>
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<td>15</td>
<td>Tibozole</td>
<td>Tablet</td>
<td>Hydroxypropyl cellulose, Polyacrylic acid</td>
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<td>Aphtach</td>
<td>Tablet</td>
<td></td>
<td>Tejin Ltd</td>
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<td>Buccastem buccal povidone</td>
<td>Tablet</td>
<td>Xanthan gum</td>
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<td>18</td>
<td>Oral – Gencrex (Phase II trials)</td>
<td>Solution</td>
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<td>Generex Biotechnology</td>
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<td>19</td>
<td>Lauriad (Phase III trials)</td>
<td>Tablet</td>
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<td>onsolis</td>
<td>Buccal film</td>
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### Mucoadhesive Polymers in Buccal Delivery Systems.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Semi-natural/natural</td>
<td>Agarose, chitosan, gelatin</td>
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<tr>
<td></td>
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<td>Hyaluronic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)</td>
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<tr>
<td></td>
<td></td>
<td>Cellulose derivatives</td>
</tr>
<tr>
<td></td>
<td>synthetic</td>
<td>[CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC] Poly(acrylic acid)-based polymers</td>
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<td></td>
<td></td>
<td>[CP, PC, PAA, copolymer of acrylic acid and PEG]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVA, PVP, thiolated polymers</td>
</tr>
<tr>
<td>Aqueous solubility</td>
<td>Water-soluble</td>
<td>CP, HEC, HPC (water&lt; 0 38C), 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></td>
<td>Cationic</td>
<td>Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan</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></td>
<td>Covalent</td>
<td>Cyanoacrylate</td>
</tr>
<tr>
<td>Potential bioadhesive forces</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>
Composition of Buccal Patches:-24-26

A. **Active ingredient.**

B. **Polymers (adhesive layer):** Hydroxy ethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.

C. **Diluents:** Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.

D. **Sweetening agents:** Sucralose, aspartame, mannitol, etc.

E. **Flavouring agents:** Menthol, vanillin, clove oil, etc.

F. **Backing layer:** Ethyl cellulose, etc.

G. **Penetration enhancer:** Cyano acrylate, etc.

H. **Plasticizers:** PEG-100, 400, propylene glycol, etc.

Methods of Preparation of Buccal Patch 26-30

(a) **Solvent casting technique**

In this technique the required quantity of mucoadhesive polymer is treated with required volume of solvent system and vortexed to allow polymer to swell. After swelling, mixture is treated with, measured quantity of plasticizer (propylene glycol or glycerin or dibutyl phthalate) and vortexed. Finally the required quantity of drug is dissolved in small volume of solvent system and added to the polymer solution and mixed well. Then set aside for some time to remove any entrapped air and transferred into a previously cleaned petri plate. The formed patches were stored in a desiccator till the evaluation tests were performed.

(b) **Hot melt extrusion technique**

The Hot-melt extrusion (HME) technique is an attractive alternative to traditional processing methods and offers many advantages over the other pharmaceutical processing techniques. Molten polymers during the extrusion process can function as thermal binders and act as drug depots and/or drug release retardants upon cooling and solidification. Since solvents and water are not necessary, the numbers of processing and time-consuming drying steps are reduced. A matrix can be massed into a larger unit independent of compression properties. The intense mixing and agitation imposed by the rotating screw cause de-aggregation of suspended particles in the molten polymer resulting in a more uniform dispersion and the process is continuous and efficient. Bioavailability of the drug substance may be improved when it is solubilized or dispersed at the molecular level in HME dosage forms. Pharmaceutical Hot-Melt Extrusion processes can be categorized as either ram extrusion or screw extrusion.

(c) **Solvent evaporation method**

In this technique the required quantity of mucoadhesive polymer is treated with required volume of solvent system and heat on water bath to dissolve polymer properly than dissolved the drug in that solution by heating and add plasticer in required quantity. Than set aside for some time to remove any entrapped air and transferred into a previously cleaned petri plate. The formed patches were stored in a desiccator till the evaluation tests were performed.
Evaluations of Buccal Patch: 30-34

1. **Surface pH:-**
   a. Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.

2. **Thickness measurements:-**
   a. The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.

3. **Swelling study:-**
   a. Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1- hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper. The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated.

   \[
   SI = \frac{(W2 - W1) \times 100}{W1}
   \]

4. **Folding endurance:-**
   The folding endurance of patches is determined by repeatedly folding 1 patch at the same place until it breaks or is folded up to 200 times without breaking.

5. **Thermal analysis study:-**
   Thermal analysis study is performed using differential scanning calorimeter (DSC).

6. **Morphological characterization:-**
   Morphological characters are studied by using scanning electron microscope (SEM).

7. **Water absorption capacity test:-**
   Circular Patches, with a surface area of 2.3 cm² are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na₂HPO₄, 0.19 g KH₂PO₄, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation.

   \[
   \text{Water uptake (\%)} = \frac{(W_w - W_i)}{W_f} \times 100
   \]
   Where,
   Ww is the wet weight and Wf is the final weight. The swelling of each film is measured.

8. **Ex-vivo bioadhesion test:-**
   The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is
tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength.

a. Measurement of mucoadhesive strength

9. **In Vitro Drug Release:**

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution. The invitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer.
1. Schematic diagram of Franz diffusion cell for buccal patch

10. Permeation study of buccal patch:-
   The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content.

11. Ex-vivo mucoadhesion 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 is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch, and drug content is noted.

12. Measurement of mechanical properties:-
   Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break. The force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula.

\[ T = \frac{m \times g \times b \times t}{B \times T} \text{ Kg/mm}^2 \]

Where,
- M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec \(^2\)
- B - is the breadth of the specimen in cm
- T - is the thickness of specimen in cm.
- Tensile strength (kg/mm\(^2\)) is the force at break (kg) per initial cross-sectional area of the specimen (mm\(^2\))

13. Stability study in human saliva:-
   The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50 years). Buccal patches are placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature controlled oven at 37°C ± 0.2°C for 6 hours.

FUTURE CHALLENGES AND OPPORTUNITIES
   The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. The relatively recent evolution of recombinant DNA research and modern synthetic and biotechnological methodologies allow the biochemist and chemist to produce vast quantities of variety of peptides and proteins possessing better pharmacological efficacy. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. The future challenge of pharmaceutical scientists will not only be polypeptide cloning and
synthesis, but also to develop effective non-parenteral delivery of intact proteins and peptides to the systemic circulation. Buccal permeation can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, chelators and cyclodextrins. Researchers are now looking beyond traditional polymer networks to find other innovative drug 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. Successfully developing these novel formulations requires assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Another important aspect concerns the in vitro and ex vivo techniques which are employed for evaluation of the performance of the materials and dosage forms. Efforts should be made to develop standard in vitro and ex vivo biological models that allow one to characterize and compare different material and formulation in terms of their capability to promote drug absorption via the buccal route.

CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Adhesions of these drug delivery devices to mucosal membranes lead to an increased drug concentration gradient at the absorption site and therefore improve bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers), to reduce the overall required dosage and minimize side effects that may be caused by systemic administration of drugs. Investigations are continuing beyond traditional polymer networks to find other innovative drug transport systems. At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of drugs used orally by manipulation of the formulation strategies like inclusion of pH modifiers, enzyme inhibitors, permeation enhances etc.

REFERENCES


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