Mucoadhesive Buccal Drug Delivery: A Potential Alternative to Conventional Therapy

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Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extended periods of time by interfacial forces1. For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue, or the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion2.

MUCA OD HESIVE DR U G DELIVERY SYSTEMS

These may be defined as drug delivery systems which utilize property of bioadhesion of certain water soluble polymers which become adhesive on hydration3 and hence can be used for targeting a drug to a particular region of the body for extended periods of time4.

The mucosal layer lines a number of regions of the body including the gastro-intestinal tract, the urogenital tract, the airways, the ear, nose and eye. These represents potential sites for attachment of any bioadhesive system and hence, the mucoadhesive drug delivery system includes the following5:

1. Buccal delivery system
2. Oral delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system.

In the following, recent advances in the delivery of drugs through mucoadhesive buccal system is reviewed, since this offers a great potential for commercial application as an alternative to conventional drug therapy.

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MUCA OD HESIVE BUCCAL DR U G DELIVERY SYSTEM

Drug delivery via the membranes of the oral cavity can be subdivided as follows6:

1. Sublingual delivery, which is the administration of drug via the sublingual mucosa to the systemic circulation.
2. Buccal delivery, which is administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation; and
3. Local delivery, for the treatment of conditions of the oral cavity, principally aphthous ulcers, fungal conditions and periodontal diseases by application of the bioadhesive system either to the palate, the gingiva or the cheek6.

These oral mucosal sites differ greatly from one another, in terms of anatomy, permeability to an applied drug, and their ability to retain a delivery system for a desired length of time. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs and is convenient, accessible and generally well accepted.

What makes the oral mucosa, mainly the buccal site rather attractive for drug delivery is the combination of several aspects7:

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1. The oral mucosa is easily accessible, so dosage forms can be easily administered and even removed from the site of application.

2. Since patients are well adapted to the oral administration of drugs in general, patient acceptance and compliance is expected to be good.

3. According to its natural function the oral mucosa is routinely exposed to a multitude of different external compounds and, therefore, is supposed to be rather robust and less prone to irreversible irritation or damage by a dosage form, its drug, excipient or additive.

4. Its ability to recover after local treatment is pronounced, and hence allows a wide range of formulations to be used; e.g., bioadhesive ointments and patches.

Local delivery of drugs to tissues of the oral cavity has a number of applications including the treatment of toothache\textsuperscript{10}, periodontal diseases\textsuperscript{11,15}, dental caries\textsuperscript{13}, bacterial\textsuperscript{14} and fungal infections\textsuperscript{15} and aphthous stomatitis\textsuperscript{16,17}.

Conventional formulations for local oral delivery are principally lozenges, troches, mouth paints, mouth washes, oral gels, pastes and suspensions\textsuperscript{5,8,18}. Release of drug from these preparations involves an initial burst of activity, whose level rapidly declines to subtherapeutic concentrations. A conventional lozenge formulation produces effective levels of drug locally in the mouth for a period of less than one hour and repeated administration is usually limited to a maximum of less than 10 units per day because of the systemic toxicity due to the large quantity of drug swallowed. Apart from compliance problems involved in frequent administration, such products are unsuitable for effective therapy overnight. Also conventional lozenges tend to increase salivary flow when sucked, thereby reducing local drug concentration and residence time in the mouth\textsuperscript{14}. Moreover, administration of conventional buccal and sublingual tablets and capsules does not go along with drinking and eating and is, at least, a handicap for speaking, so any administration is restricted to rather limited periods of time and controlled release is not within the scope of such formulations\textsuperscript{5}.

Mouthwashes have an even more transient effect than lozenges, while oral gels, pastes and suspensions are difficult to be retained in the mouth and have poor patient acceptability\textsuperscript{19}.

**ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS**

Drug administration via the oral mucosa offers several advantages\textsuperscript{5,20,22}

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localisation of the drug to the oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients.
5. Offers an excellent route for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
6. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
7. 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 ionised species can be achieved.
8. 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.
9. Drugs which show poor bioavailability via the oral route can be administered conveniently.
10. It offers a passive system for drug absorption and does not require any activation.
11. The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up, beneath the applied dosage form.
12. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.

**LIMITATIONS OF BUCCAL DRUG ADMINISTRATION**

Drug administration via this route has certain limitations\textsuperscript{20,22}.
1. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an abnoxious odour cannot be administered by this route.

2. Drugs which are unstable at buccal pH cannot be administered by this route.

3. Only drugs with a small dose requirement can be administered.

4. Drug contained in the swallowed saliva follows the peroral route and advantages of buccal route are lost.

5. Only those drugs which are absorbed by passive diffusion can be administered by this route.

6. Eating and drinking may become restricted.

7. There is an ever present possibility of the patient swallowing the tablet.

8. Over hydration may lead to formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers23.

ANATOMY OF THE ORAL CAVITY

The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane of a highly-vascularized nature. Drug penetrating into the membrane can find access to the systemic circulation via net of capillaries and arteries lying underneath7.

The epithelium of the oral cavity is in principle similar to that of the skin, with interesting differences regarding keratinization and the protective and lubricant mucus spread across its surface. It can be divided into three functional zones:

1. The mucus-secretory regions consisting of the soft palate, the floor of the mouth, the underside of the tongue, and the labial and buccal mucosa, which have a normally non-keratinized epithelium.

2. The hard palate and the gingiva are the regions of the masticatory mucosa and have a normally keratinized epidermis.

3. Specialized zone consisting of the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

As the stratum corneum may be a potential barrier to mucosal penetrations, drugs are traditionally placed at the non-keratinized sites like the buccal and sublingual regions24.

A. The Mucus Layer:

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 humans4. 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 state21. However, it has the following general composition23:

1. Water - 95%
2. Glycoproteins and Lipids - 0.5 to 5%
3. Mineral Salts - 1%
4. Free proteins - 0.5 to 1%

B. Functions of mucus layer:

The primary functions of the mucus layer are2:

1. Protective: resulting particularly from its hydrophobicity.

2. Barrier: the role of the mucus layer as a barrier in tissue absorption of drugs and other substrates is well known as it influences the bioavailability of drugs.

3. Adhesion: mucus has strong cohesional properties and firmly binds to the epithelial cell surface as a continuous gel layer.

4. Lubrication: an important role of the mucus layer is to keep the mucosal membrane moist. Continuous secretion of mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulfate residues and this high charge density due to negative charge contributes significantly to bioadhesion25.
C. The Salivary Secretion:

Besides the mucus, the mucosal layer of the oral cavity is kept moist by the saliva secreted mainly by three pairs of salivary glands namely the submaxillary, the parotid and the sublingual glands. The pH of the salivary secretion ranges from about 6.2 to 7.4 with an average of 6.6. About 1.5 litres of saliva is secreted per day.26

There is a considerable variation in the individual saliva flow rates. It ranges from 0.21 to 1.18 ml/min, with a mean of 0.65 ml/min. under the resting condition27 and 0.56 to 2.70 ml/min. with a mean of 1.63 ml/min. under exogenously stimulated conditions28.

Mechanism of Bioadhesion

For bioadhesion to occur, a succession of phenomena, whose role depends on the nature of the bioadhesive, is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface, or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the service of the tissue surface of interpenetration of the chains of the bioadhesive with those of the mucus takes place. Low chemical bonds can then settle25.

On a molecular level, muco-adhesion can be explained based on molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions arise from van der waals forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive interactions occur because of electrostatic and steric repulsion. For muco-adhesion to occur, the attractive interaction should be larger than nonspecific repulsion.

Several theories have been proposed to explain the fundamental mechanism(s) of adhesion1,21,26,29. In a particular system, one or more theories can equally well explain or contribute to the formation of bioadhesive bonds.

FACTORS AFFECTING BIOADHESION

The bioadhesive power of a polymer or of a series of polymers is affected by the nature of the polymer and also by the nature of the surrounding media4,21,26. Polymer-related factors include molecular weight, concentration of active polymer, flexibility of polymer chains and spatial conformation of the polymer molecule. Environment-related factors which have been found to influence bioadhesion include the pH of the polymer-substrate interface, the pressure initially applied to the bioadhesive tissue contact site as well as the initial contact time between bioadhesives and the mucus layer. The selection of the model substrate surface also influences the determination of bioadhesion. Physiological factors like mucin turnover rate and the condition of the mucosal layer (normal or diseased) also have a bearing on the bioadhesion.

REPORTED MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS

Probably, the first oral adhesives used in the mouth were developed in dental practice, in the late 1950’s. One example is the ‘Orahesive Bandage’ composed of gelatin, sodium carboxymethyl cellulose and polyisobutylene 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 and Cyr. In the early 1980’s the systematic investigation on mucoadhesives began and several excellent mucoadhesives were identified.

A lot of work has since been done on the development of mucoadhesive buccal drug delivery systems (Table-1) both for systemic and local use. Various devices in the form of single and multilayered tablets, laminated patches, adhesive films, ointments and gels have been developed using various bioadhesive polymers. However, the method of formulation used and described has mainly been on a laboratory scale.

METHODS USED TO STUDY BIOADHESION

Several test methods have been reported for studying bioadhesion. These tests are necessary not only to screen a large number of candidate mucoadhesives, but also to study their mechanisms. These tests are also important during the design and development of a bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis and bioadhesive bond strength. The test methods can broadly be classified into two major categories:

I. In vitro / ex vivo methods

II. In vivo methods
1) **In vitro lex vivo methods**: Most in vitro methods are based on the measurement of either tensile or shear stress. Bioadhesiveness determined by measurement of stress tends to be subjective since there is no standard test method established for bioadhesion.

1. Methods based on measurement of tensile strength

These methods usually measure the force required to break the adhesive bond between a model membrane and the test polymer. The instruments usually employed are modified balances or tensile testers. A typical example is the method employed by Robinson and his group. In this method, the force required to separate the bioadhesive sample from freshly excised rabbit stomach tissue was determined using a modified tensiometer. A section of the tissue, having the mucus side exposed, was secured on a weighed glass vial placed in a beaker containing USP simulated gastric fluid. Another section of the same tissue was placed over a rubber stopper again with the mucus side exposed and secured with a vial cap and a small quantity of polymer was placed between the two mucosal tissues. The force used to detach the polymer from the tissue was then recorded. The results of the study provided important information regarding the effects of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure on bioadhesion. A number of workers have used test methods based on measurement of tensile strength for the determination of bioadhesion.

2. Methods based on measurement of shear strength

The shear stress measures the force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. An example is the Wilhelmy plate method reported by Smart et al. The method uses a glass plate suspended from a microbalance which is dipped in a temperature controlled mucus sample and the force required to pull the plate out of the solution is determined under constant experimental conditions.

3. Other in vitro methods

A number of other methods including electrical conductance and thumb test method, adhesion weight method, fluorescent probe method, flow channel method, falling liquid film method, colloidal gold staining method, viscometric method and mechanical spectroscopic method have been used for the determination of bioadhesion.

In spite of a number of methods for the determination of bioadhesion, a poor co-relation has been found between the bioadhesive strength measured in vitro and the bioadhesive performance in vivo, using some of these methods. It has been found that two formulations exhibiting similar bioadhesive strength determined using the conventional 'stress-strain' method, in vitro exhibit different adhesion time in vivo. The difference might be due to different erosion resistance of the formulations or due to premature dislodgement of the formulations due to excessive swelling and formation of slippery surface.

Recently, two apparatuses have been described for the in situ evaluation of bioadhesive properties of buccal tablets. The apparatus mimics the conditions of the buccal cavity and use membranes as model mucosal membrane for studying the bioadhesive properties.

II. **In vivo methods**

Various methods for in vivo evaluation of both placebo and drug containing mucoadhesive devices in healthy human volunteers has been described in the literature.

Rathbone et al. have discussed several methods to study the rate and extent of drug loss from human oral cavity. These include the buccal absorption test, disks methods and perfusion cells. These methods have provided information on the mechanisms by which drugs are transported across oral cavity membranes.

In an attempt to study the influence of application site on bioadhesion and release characteristics of a bioadhesive buccal slow release tablet of miconazole, Bouckaert et al. found gingiva to be the best site among palate, cheek and gingiva.

A high inter-individual variability with respect to the drug release and adhesion time of buccal tablets has been observed during in vivo studies, which has been attributed to variation in individuals with respect to the salivary flow rate, the oral anatomy and the individual movement pattern of the mouth.
Table 1: Some reported mucoadhesive buccal drug delivery systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Action</th>
<th>Mucoadhesive polymers</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Tablet</td>
<td>Systemic</td>
<td>CP-934, HPC-H</td>
<td>32</td>
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<td>Lidocaine</td>
<td>Mutilayered Tablet</td>
<td>Local</td>
<td>CP-934, HPC-H</td>
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<td>Prednisolone</td>
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<td>Local</td>
<td>CP-934</td>
<td>16</td>
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<tr>
<td>Protirelin</td>
<td>Laminated patches</td>
<td>Systemic</td>
<td>HEC, HPC, PVP, PVA</td>
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<td>Tretinoin</td>
<td>Ointment</td>
<td>Systemic</td>
<td>Poly methacrylic methyl ester</td>
<td>33</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>Bilayered tablet</td>
<td>Local</td>
<td>CP-934, HPC</td>
<td>34, 35</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Film</td>
<td>Local</td>
<td>HPC</td>
<td>36</td>
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<td>Metronidazole</td>
<td>Tablet</td>
<td>-</td>
<td>CP-934, HPC</td>
<td>37, 38</td>
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<td>Betamethasone</td>
<td>Tablet</td>
<td>Local</td>
<td>Na CMC</td>
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<td>Cetyl pyridinium chloride</td>
<td>Tri-layered tablet</td>
<td>Local</td>
<td>CP-934, HPC</td>
<td>14</td>
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<td>Sodium fluoride</td>
<td>Slow release tablet</td>
<td>Local</td>
<td>Modified starch CP-934</td>
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<td>CP-940, HPC</td>
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<td>Chitosan</td>
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<td>Verapami HCl</td>
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<td>CP-934, HPC-M</td>
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<td>Local</td>
<td>Modified starch CP-934</td>
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<td>PAA, PVP</td>
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<td>Triamcinolone acetonide</td>
<td>Ointment for oral mucosa</td>
<td>Local</td>
<td>Methacrylic acid Methacrylic acid methyl ester</td>
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<td>Drug</td>
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<td>Action</td>
<td>Mucoadhesive polymers</td>
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<td>Discs</td>
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<td>CP-907, CP-941</td>
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<td>Sodium alginate, PEG-6000</td>
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<td>Nifedipine</td>
<td>Film</td>
<td>Systemic</td>
<td>Sodium alginate methyl cellulose, PVP, PEG-6000</td>
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<td>Buprenorphine</td>
<td>Patch</td>
<td>Systemic</td>
<td>CP-934</td>
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<td>Hydralazine HCl</td>
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<td>Tablet</td>
<td>Systemic</td>
<td>Chitosan, Sodium alginate</td>
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<td>Film</td>
<td>Systemic</td>
<td>HPC, HPMC phthalate</td>
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<td>CP-974P, HPMC-K4M, PEG-6000</td>
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<td>Film</td>
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<td>HPC-M, CP-934P</td>
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**KEY:**

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<thead>
<tr>
<th>Abbreviation</th>
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<td>CMC</td>
<td>Carboxymethylcellulose</td>
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<tr>
<td>CP</td>
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<td>Hydroxypropylcellulose</td>
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<tr>
<td>HPMC</td>
<td>Hydroxypropylmethylcellulose</td>
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<td>PADH</td>
<td>Poly (acrylic acid - 2, 5 - dimethyl - 1, 5 - hexadienc)</td>
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<tr>
<td>PEG</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
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<td>Polyvinyl alcohol</td>
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<td>Polyvinyl Pyrrolidone</td>
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<td>Drug</td>
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<tr>
<td>Clotrimazole</td>
<td>Tablet, Film</td>
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Methods used for in vitro release studies

No standard in vitro method has yet been developed for the dissolution studies of buccal formulations. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. A description of the apparatus and the testing conditions used is given in Table 2.

CONCLUSION

It can be said that drug delivery using mucoadhesive buccal formulations offers a great potential both for systemic and local use. A number of drug candidates have shown potential for use in mucoadhesive devices. There is a need for analysing the viability of such devices on an industrial scale and the willingness of the industry to take up potential candidates so as to offer an alternative to conventional drug therapy.

REFERENCES