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# Muco/Bioadhesive Polymers in Buccal Drug Delivery- A Review

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## ABSTRACT

Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s. Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs. This review highlights the use of mucoadhesive polymers in buccal drug delivery the mucosa of the oral cavity presents a formidable barrier to drug penetration and one method of optimizing drug delivery is by the use of adhesive dosage forms. Mucosal adhesive materials are hydrophilic macromolecules containing numerous hydrogen-bonds –forming groups. They have been called “wet” adhesives in that they require moisture to become adhesive and this may be supplied by the saliva: the latter may also acts as the dissolution medium. Various buccal-adhesive formulations have been investigated with a view to delivering drugs locally or systematically. We focus on the new generation of mucoadhesive polymers such as thiolated polymers, followed by the recent mucoadhesive formulations for buccal drug delivery.

**Keywords:** Buccal drug delivery, mucoadhesive polymer, mucoadhesion

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## INTRODUCTION

The buccal route has the advantage of allowing excellent accessibility, reasonable patient acceptance and compliance, avoids first-pass metabolism and involves a relatively robust mucosa. The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic 'first-pass' effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. Other routes, such as nasal, ocular, pulmonary, rectal, and vaginal drug administration, have provided excellent opportunities for the delivery of a variety of compounds. However, the mucosal lining of the oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery. Avoiding acid hydrolysis in the gastrointestinal (GI) tract and bypassing the 'first-pass' effect are some of the advantages of this route of drug delivery. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa are among the other advantages of this route of drug delivery.

The disadvantages associated with this route of drug delivery are the low permeability of the buccal membrane[1], specifically when compared to the sublingual membrane[2,3], and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 $cm^2$, of which ~50 $cm^2$ represents non-keratinized tissues, including the buccal membrane[4]. The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug[3]. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. These are some of the problems that are associated with buccal drug delivery. Moreover, the hazard of choking by involuntarily swallowing the delivery system is a concern, in addition to the inconvenience of such a dosage form when the patient is eating or drinking.

### Oral Mucosa

Buccal region is that part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Numerous racemose, mucous, or

serous glands are present in the submucous tissue of the cheeks[5]. The buccal glands are placed between the mucous membrane and buccinator muscle: they are similar in structure to the labial glands, but smaller. About five, of a larger size than the rest, are placed between the masseter and buccinators muscles around the distal extremity of the parotid duct; their ducts open in the mouth opposite the last molar tooth. They are called molar glands[6]. Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm2) than that in the sublingual, gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500–800 μm and is rough textured, hence suitable for retentive delivery systems[7]. The turnover time for the buccal epithelium has been estimated at 5–6 days[8].

Buccal mucosa composed of several layers of different cells as shown in Figure. The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40–50 cell layers thick[4]. Lining epithelium of buccal mucosa is the non-keratinized stratified squamous epithelium that has thickness of approximately 500–600 μ and surface area of 50.2 $cm^2$. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer[9]. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. Lipid analysis of buccal tissues shows the presence of phospholipid 76.3%, glucosphingolipid 23.0% and ceramide NS at 0.72%. Other lipids such as acyl glucosylated ceramide, and ceramides like Cer AH, Cer AP, Cer NH, Cer AS, and EOHP/NP are completely absent [10].

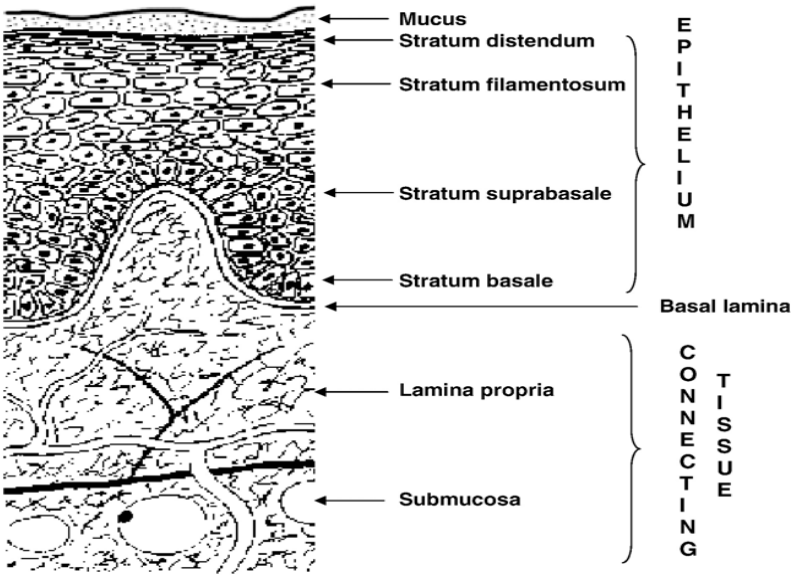


**Figure 1:Cross section of buccal mucosa**

The primary function of buccal epithelium is the protection of the underlying tissue. In nonkeratinized regions, lipid-based permeability barriers in the outer epithelial layers protect the

underlying tissues against fluid loss and entry of potentially harmful environmental agents such as antigens, carcinogens, microbial toxins and enzymes from foods and beverages[11].

**Mucoadhesion/Bioadhesion**

**Definition**

In 1986, Longer and Robinson defined the term 'bioadhesion' as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface[12]. The general definition of adherence of a polymeric material to biological surfaces (bioadhesives) or to the mucosal tissue (mucoadhesives) still holds.

**Theories of bioadhesion**

Five theories have been suggested to play a major role in bioadhesion, namely, adsorption, diffusion, electronic, fracture, and wetting theories [13,14]. In the 'adsorption theory', primary and secondary chemical bonds of the covalent and non-covalent (electrostatic and van der Waals' forces, hydrogen, and hydrophobic bonds) types are formed upon initial contact between the mucus and the mucoadhesive polymer. Most of the initial interfacial bonding forces are attributed to non-covalent forces. The formation of secondary chemical bonds greatly depends on properties of the polymer, which will be covered briefly in the next section. The basis of the 'diffusion theory' is chain entanglement between glycoproteins of the mucus and the mucoadhesive polymer. Upon initial contact between these two polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and the diffusion coefficient of the bioadhesive polymer are among the factors which influence the inter-diffusion of the macromolecule network.

The third theory is the 'electronic theory'. Because of different electronic properties of the mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occurs. Electron transfer contributes to formation of a charged double layer at the interface of the mucus and the polymer, which results in forces of attraction in this region and inter diffusion of the two surfaces. The 'fracture theory' relates the force required for the detachment of polymers from the mucus to the strength of their adhesive bond. It has been found that the work fracture is greater when the network strands are longer or the degree of cross-linking is reduced [15]. Finally, the 'wetting theory' describes the ability of a bioadhesive polymer to spread on biological surfaces. This theory is predominantly applicable to liquid bioadhesive systems. Moderately wettable polymers have been shown to exhibit optimal adhesion to human endothelial cells [16].

FACTORS AFFECTING MUCOADHESION IN THE ORAL CAVITY

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. A variety of factors affect the mucoadhesive properties of polymers, such as molecular weight, flexibility, hydrogen bonding capacity, cross-linking density, charge, concentration, and hydration (swelling) of a polymer, which are briefly addressed below.

**Polymer-related factors**

**Molecular weight:**

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000[17]. As one example, the direct correlation between the bioadhesive strength of polyoxyethylene polymers and their molecular weights, in the range of 200,000 to 7,000,000, has been shown by Tiwari et al[18].

**Flexibility:**

Bioadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. A recent publication demonstrated the use of tethered poly (ethylene glycol) – poly (acrylic acid) hydrogels and their copolymers with improved mucoadhesive properties[19]. The increased chain interpenetration was attributed to the increased structural flexibility of the polymer upon incorporation of poly (ethylene glycol). In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network[20].

**Hydrogen bonding capacity:**

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds[21]. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity[13].

**Cross-linking density:**

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross linking are three important and interrelated structural parameters of a polymer network[20]. Therefore, it seems reasonable that with increasing density of cross-linking,

diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin[20]. Flory[22] has reported this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer.

**Charge:**

Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion[13]. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium[23]. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties[24].

**Concentration:**

The importance of this factor lies in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable .[13] In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an 'unperturbed' state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties. One of the studies addressing this factor demonstrated that high concentrations of flexible polymeric films based on polyvinylpyrrolidone or poly (vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer[25]. On the contrary, it decreased the desired strength of mucoadhesion.

**Hydration (swelling)**

Hydration is required for a mucoadhesive polymer to expand and create a proper 'macromolecular mesh' [20] of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network[20]. However, a

critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs[13].

**Environmental factors**

The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer. Saliva, as a dissolution medium, affects the behavior of the polymer. Depending on the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5[26]. The pH of the microenvironment surrounding the mucoadhesive polymer can alter the ionization state and, therefore, the adhesion properties of a polymer**.** Mucin turnover rate is another environmental factor. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats[27] and 12–24 h in humans [28]. Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the oral cavity. Movements within the oral cavity continue even during sleep, and can potentially lead to the detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is necessary in order to avoid many of these interfering factors[29].

MUCOADESIVE POLYMERS

In general, adhesive polymers can be classified as synthetic vs. natural, water-soluble vs. water insoluble, and charged vs. uncharged polymers. Examples of the recent polymers classified in these categories are listed in Table 1. Natural bioadhesive macromolecules share similar structural properties with the synthetic polymers. They are generally linear polymers with high molecular weight, contain a substantial number of hydrophilic, negatively charged functional groups, and form three-dimensional expanded networks[30].. In the class of synthetic polymers, poly(acrylic acid), cellulose ester derivatives, and polymethacrylate derivatives are the current choices. Chitosan and examples of various gums, such as guar and hakea (from Hakea gibbosa), are classified as semi-natural/natural bioadhesive polymers. Poly(acrylic acid), a linear or random polymer, and polycarbophil, a swellable polymer, represent water-soluble and water-insoluble polymers, respectively. The charged polymers are divided into cationic and anionic polymers, such as chitosan and polycarbophil, respectively, while hydroxypropylcellulose is an example of uncharged bioadhesive polymers[31].

**Table -1 Mucoadhesive polymers in buccal delivery**

| Criteria | Categories | Example |
|---|---|---|
| source | semi-natural | Agarose, chitosan, gelatin, Hyaluronic acid Various gums,(guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate) |
| | Synthetic | **Cellulose derivatives** [CMC, thiolated CMC, sodium CMC, HEC,HPC, HPMC, MC,methylhydroxyethylcellulose] **Poly(acrylic acid)-based polymers** [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate),poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG] Others, Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene, PVA, PVP, thiolated polymers |
| Aqueous solubility | Water soluble | CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC,sodium alginate |
| | Water insoluble | Chitosan (soluble in dilute aqueous acids), EC, PC |
| | Cationic | Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, Trimethylated Chitosan |
| | Anionic | Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC,xanthan gum |
| | Nonionic | Hydroxyethyl starch, HPC, poly(ethylene oxide),PVA, PVP, scleroglucan |
| Potential bioadhesive forces | Covalent | Cyanoacrylate |
| | Hydrogen bond | Acrylates, PVA |
| | Electrostatic interaction | Chitosan |

NEW GENERATION OF MUCOADHESIVE POLYMERS

In a recent mini-review by Lee et al.[31], current bioadhesive polymers are classified as ‘first generation’ and ‘second generation’. The older generation of mucoadhesive polymers, referred to as boff-the shelf polymers, lack specificity and targeting capability. They adhere to the mucus non-specifically, and suffer short retention times due to the turnover rate of the mucus. The chemical interactions between mucoadhesive polymers and the mucus or tissue surfaces are generally non-covalent in nature, and are classified as consisting mostly of hydrogen bonds, hydrophobic, and electrostatic interactions (Table 1). However, newer polymers are capable of forming covalent bonds with the mucus and the underlying cell layers, and hence, exhibit improved chemical interactions.

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.

**Thiolated mucoadhesive polymers**

Through a covalent attachment between a cysteine (Cys) residue and a polymer of choice, such as polycarbophil[32], poly(acrylic acid)[33], and chitosan[34] a new generation of mucoadhesive polymers have been created. The modified polymers, which contain a carbodiimide-mediated thiol bond, exhibit much-improved bioadhesive properties. Investigations of the GI epithelial mucus have clarified the structure of this gel-like biopolymer[35]. With more than 4500 amino acids, the enormous polypeptide backbone of mucin protein is divided into three major subunits; tandem repeat array, carboxyl and amino-terminal domains. The carboxyl-terminal domain contains more than 10% of cysteine residues. The amino-terminal domain also contains Cys-rich regions. The Cys-rich sub-domains are responsible for forming the large oligomers of mucin through disulfide bonds[36]. Based on the disulfide exchange reaction, disulfide bonds between the mucin glycoprotein and the thiolated mucoadhesive polymer can potentially be formed, which results in a strong covalent interaction[37]. Other improved mucoadhesive properties of the thiolated polymers, such as improved tensile strength, high cohesive properties, rapid swelling, and water uptake behavior, have made them an attractive new generation of bioadhesive polymers.

**Target-specific, lectin-mediated bioadhesive polymers**

The possibility of developing a bioadhesive polymer which is able to selectively create specific molecular interactions with a particular target, such as a receptor on the cell membrane of a specific tissue, is a very attractive potential for targeted delivery. The potential of a specific receptor–bioadhesive polymer interaction can circumvent the limiting factors of rapid mucus turnover and short residence time. Unlike general mucoadhesive polymers, which bind to the mucosal surface ubiquitously, a specific receptor mediated interaction with the mucosal surface could allow for direct binding to the cell surface, rather than only the mucus layer. Specific proteins or glycoproteins, such as lectins, which are able to bind certain sugars on the cell membrane, can increase bioadhesion and potentially improve drug delivery via specific binding

and increase the residence time of the dosage form. This type of bioadhesion should be more appropriately termed as cytoadhesion[36]. This represents one example of lectin used as a cell adhesion marker rather than a targeted delivery vehicle to the buccal cavity. Nevertheless, lectin mediated bioadhesive polymers, as second-generation bioadhesives, contain an enormous potential for drug delivery.

DEVELOPMENTS IN BUCCAL ADHESIVE DRUG DELIVERY

Retentive buccal mucoadhesive formulations may prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Buccal adhesive drug delivery systems using matrix tablets, films, layered systems, discs, micro spheres, ointments and hydrogel systems has been studied and reported by several research groups. However, limited studies exist on novel devices that are superior to those of conventional buccal adhesive systems for the delivery of therapeutic agents through buccal mucosa.

An ideal buccal adhesive system must have the following properties:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in an unidirectional way toward the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

**Commercial buccal adhesive drug delivery systems**

Recent reports suggest that the market share of buccal adhesive drug delivery systems are increasing in the American and European market with the steady growth rate of above 10%. .

**Table -2 Commercially Available Buccal Adhesive Formulations**

| Commercial name | Bioadhesive polymer | Company | Dosage form |
|---|---|---|---|
| Buccastem | PVP,Xanthum gum, Locust bean gum | Rickitt Benckiser | Tablet |
| Suscard | HPMC | Tablet | Tablet |
| Gavison liquid | Sodium alginate | Benckiser | Oral liquid |
| Orabase | Pectin, gelatin | ConvaTech | Oral paste |
| Luborant | Sodium CMC | Antigen | Artificial saliva |
| Saliveze | *Sodium CMC* | Wyvern | Artificial saliva |
| Corlan pellets | *Acasia* | Celltech | Oromucosal pellets |

RESEARCH ON BUCCAL ADHESIVE DRUG DELIVERY SYSTEMS

Several buccal adhesive delivery devices were developed at the laboratory scale by many

researchers either for local or systemic actions. They are broadly classified into:

- ❖ Solid buccal adhesive dosage forms
- ❖ Semi-solid buccal adhesive dosage forms
- ❖ Liquid buccal adhesive dosage forms

**Solid buccal adhesive formulations**

Dry formulations achieve bioadhesion via dehydration of the local mucosal surface.

**Tablets**:

Several bioadhesive tablet formulations were developed in recent years either for local or systemic drug delivery. Tablets that are placed directly onto the mucosal surface have been demonstrated to be excellent bioadhesive formulations. However, size is a limitation for tablets due to the requirement for the dosage form to have intimate contact with the mucosal surface. These tablets adhere to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectionally targeting buccal mucosa or mutidirectionally in to the saliva. Table 3. represents some of the research done so far in the development of buccal adhesive tablets.

Microparticles. Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a lager mucosal surface area. In addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity. The small size of microparticles compared with tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral cavity is reduced.

**Wafers**:

Bromberg et al.[38] described a conceptually novel periodontal drug delivery system that is intended for the treatment of microbial infections associated with peridontitis. The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers.

**Lozenges**:

Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. Conventional lozenges produce a high initial release of drug in the oral cavity, which rapidly declines to subtherapeutic levels, thus multiple daily dosing is required. A slow release bioadhesive lozenge offers the potential for prolonged drug release with improved patient compliance. Codd and Deasy investigated bioadhesive lozenges as a means to deliver antifungal agents to the oral cavity [39].

**Table-3 Buccal adhesive tablets**

| Buccal adhesive tablets | Drug Bioadhesive polymer | Reference |
|---|---|---|
| Ketoprofen | Chitosan and sodium alginate | [41] |
| Nifedipine | Chitosan, polycarbophil, sodium alginate, gellan gum | [42] |
| Propranolol | HPMC, CP 934 | [43] |
| Propranolol | HPMC, PC | [44] |
| Diltiazem | CP 934 and PVP K-30, citric acid, and PEG4000 | [45] |
| Metaclopromide | *CP,HPMC,PC,SCMC,PAA* | [46] |
| Metronidazole | CP-934, HPMC | [46] |
| Nystatin | Carbomer ,HPMC | [47] |
| Lidocaine | CP-934,HPC-H | [48] |
| Omeprazole | Sodium alginate, HPMC, CP-934, PC | [49] |
| Nicotine | HPC, CP-934P, PVP | [50] |
| Pentazocine | CP-934p,HPMC | [51] |

Abbreviations: CP: carbapol, HPMC: hydroxyl propyl methyl cellulose, PC: polycarbophil, SCMC: sodium carboxy methyl cellulose, PAA:polyacrylicacid, HPC: Hydroxy propyl cellulose, PVP: poly(vinylpyrrolidine)

**Semi-solid dosage forms**

**Gels**:

Gel forming bioadhesive polymers include crosslinked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs. Gels have been widely used in the delivery of drugs to the oral cavity. Advantages of gel formulations include their ability to form intimate contact with the mucosal membrane and their rapid release of drug at the absorption site. A limitation of gel formulations lies on their inability to deliver a measured dose of drug to the site. They are therefore of limited use for drugs with narrow therapeutic window. He et al.[40] designed a novel, hydrogel based, bioadhesive, intelligent response system for controlled drug release. This system combined several desirable facets into a single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethyleneoxide) to promote mucoadhesion.

**Patches/films**:

Flexible films may be used to deliver drugs directly to a mucosalmembrane. They also offer advantages over creams and ointments in that they provide ameasured dose of drug to the site. Buccal adhesive films are already in use commercially for example, Zilactin used for the therapy of canker sores, cold sores and lip sores.

**Liquid dosage forms**

Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface. Traditionally, pharmaceutically acceptable polymers were used to enhance the viscosity of products to aid their retention in the oral cavity. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer.

## CONCLUSION

In conclusion, the oral mucosa's accessibility, high blood supply, by-pass of the hepatic first pass metabolism, quick recovery time after damage and permeability profile makes it an attractive and interesting area for topical drug delivery research. There are several challenges to overcome, which include the permeability barrier of the epithelium and enzymatic activity within the oral cavity which can degrade biological drugs. With the appropriate technologies and delivery techniques the oral mucosa could, in the future, be utilised for the treatment of many diseases both mucosal and systemic and the catalogue of drugs which can be delivered via the mucosa could be greatly increased. Further advances in mucobuccal adhesive technology and sustained local drug release also have the potential for reducing the systemic side effects from ingested or injected therapies, where an oral mucosal disease is the target of therapy.

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