Review Article

An overview of applications of mucoadhesive buccal film in Oral Medicine

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ABSTRACT

The mucosal covering of the oral cavity connects the external environment to interior of the body. This mucosal barrier, however subjected to different types of pathologies which require local treatment such as gingivitis, periodontal disease, oral candidiasis, herpes and aphthous ulcers. Amongst the diverse routes of drug delivery, oral route is the most desirable and is convenient to both clinician and patient. Since oral administration of drugs have certain limitations such as drugs undergoing first pass metabolism and enzymatic degradation within the gastrointestinal tract, limits oral bioavailability of drugs. For this reason, several buccal formulations like gels, mucoadhesive tablets , patches and buccal films have been developed that allow direct contact with the oral mucosa and provide a prolonged release of the drug, reducing the need for frequent drug doses.

Key words: *adhesion, bioavailability mucoadhesive buccal film, oral mucosa, patch*

Oral mucosa is one of the most acceptable and convenient route of drug administration. This route offers many advantages when compared to other routes such as preventing enzymatic degradation of the drug molecules in the gastrointestinal tract by passing hepatic first pass metabolism and good patient acceptance when compared to ocular, nasal, rectal, and vaginal routes. Since oral mucosa has a larger surface area, it can permeate low molecular weight drugs through mucosal epithelium quickly when compared to ocular and nasal routes [1]. Buccal drug delivery system is well accepted by patients as the buccal cavity is easily accessible for self-medication. In addition, buccal dosage forms allow drug absorption to be rapidly terminated in case of an adverse reaction. Formulations of buccal dosage forms include adhesive tablets, gels, and patches of which patches are preferable in terms of flexibility and comfort. In this review we discuss the applications of mucoadhesive buccal films in Oral Medicine.

Mucoadhesive films have enough flexibility and elasticity which provide greater comfort to patient. However, they are strong enough to resist breakage caused by movements of the mouth. Due to these features, films can also be used during sleep, increasing adherence to treatment [2]. They can be formulated using natural polymers, pectin and gellan gum. Pectin is a natural polysaccharide found in the cell wall of several plant species, mainly composed by alternating galacturonic acid, rhamnose residues, and some arabinan and/or galactan side chains. It has both mucoadhesive and swelling properties, can be used either alone or associated with natural or synthetic polymers in designing of different drug delivery system. Gellan gum is an exocellular polysaccharide secreted from the bacterium *Sphingomonas elodea* and consists of repeating tetrasaccharide of glucuronic acid, rhamnose, and glucose [3].

MECHANISM OF MUCOADHESION

Buccal film adhere to the oral mucosa through the mechanism of mucoadhesion. Contact between a pressure-sensitive adhesive material and a surface is called as adhesion, which can be defined as the state in which two surfaces are attached together due to valence interfacial

forces or interlocking action or both. Bio adhesion is an adhesion of a synthetic or natural material to biological surface while mucoadhesion is adhesion of material to mucus and/ or an epithelial surface [4, 5]. Various mucoadhesive polymers have been investigated and identified are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups, and will hydrate and swell when placed in contact with an aqueous solution [6]. Mucoadhesion occurs in two stages depending on nature of dosage form and its delivery.

- **Stage I (Contact Stage):** Due to wetting, spreading and swelling of the bio adhesive surface, a close contact is created between a bio adhesive film and a membrane. Sometimes additional forces like mechanical system in vaginal delivery, aero dynamics in nasal delivery and peristaltic motions in intestinal delivery of dosage form help in this stage [7].
- **Stage II (Consolidation Stage):** Moisture breaks molecules and inter penetration or dominant attractive interaction between two surfaces starts due to Vander walls forces, electrostatic attractions, hydrogen bonding and hydrophobic interactions. For complete bio-adhesion attractive forces must overcome repulsive forces.

Consolidation step is further explained by two theories [8]. Diffusion theory states that mucus glycol proteins interact with the mucoadhesive molecules by interpenetrating their chains and forming secondary bonds. This is a chemical as well as mechanical interaction. Whereas, according to dehydration theory, after contact with mucus, material undergoes dehydration until osmotic pressure balance and jelly mixture of mucus with material is obtained. Solid or hydrated formulation does not work by this theory [9].

BUCCAL DRUG DELIVERY

Oral cavity comprises of lips, tongue, cheek, soft and hard palate, gingiva and floor of the mouth. Oral mucosal layer consist of three layers: outer epithelium, middle basement and inner connective tissues. 100cm total area of the oral cavity consists of about one third of buccal surface of 0.5mm thickness epithelium [10]. The oral mucosa is robust and shows short recovery time after stress or damage. Drug absorption is facilitated by the continuous washing action of saliva (0.5-2 liters per day) over the mucosal surface. In case of an adverse drug reaction, the route offers easy removal of the drug. Furthermore, the drug is not subjected to the acidic environment of the stomach, therefore adequate therapeutic serum concentrations of some drugs can be achieved more rapidly.

It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. The order of permeability of the oral mucosa is sublingual>buccal>palatal which depends on relative thickness and degree of keratinization [11]. Non-keratinized region of oral mucosa is most suitable region for drug administration especially proteins/peptides than nasal, rectal and vaginal drug delivery. Drug enters into systemic circulation through jugular ducts via network of blood vessels [12]. Intercellular spaces and cytoplasm of oral mucosa being hydrophilic acts as a barrier for lipophilic compounds while cell membrane being lipophilic acts as a barrier for hydrophilic compounds [13]. To overcome this problem of penetration of high molecular weight compounds, absorption efficiency can be enhanced by few chemicals like fatty acids, bile salts and surfactants such as sodium dodecyl sulfate which are called as absorption enhancers [14]. Physical characteristics and drug concentrations of mucoadhesive buccal film are explained in table 1 and 2 respectively.

Table 2: Drug concentrations in mucoadhesive buccal film [15]

Drug	Example	Dose(mg)
Anti-histaminics	Levocetrizine Loratidine	5, 10 5
NSAIDs	Ketorolac Indomethacin Valdecoxib Piroxicam Ketoprofen Flurbiprofen	10 25 10, 20 10, 20 12.5, 25 20
Opiod analgesics	Oxycodone	2.5-10
Anti-fungal	Flucanozole	2.5
Others	Nicotine	1-2

CHARACTERISTICS OF AN IDEAL BUCC0-ADHESIVE DRUG DELIVERY SYSTEM [16, 17]

- Safe and nontoxic.
- Sufficient patient compliance without hampering normal functions such as talking, eating and drinking.
- Good mechanical strength.
- Immediate adherence to the buccal mucosa.
- Controlled drug release.
- Optimum drug absorption

Table 1: Physical characteristics of mucoadhesive buccal film [15]

Property/subtype	Flash release wafers	Mucoadhesive melt away wafers	Mucoadhesive sustained release
Area (cm^2)	2-8	2-7	2-4
Thickness µm	20-70	50-500	50-250
Structure (Film)	single	Single or multilayer	multilayer
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution

ADVANTAGES OF BUCCOADHESIVE DRUG DELIVERY [18]

- Drug is easily administered and extinction of therapy in emergency can be facilitated.
- Drug release for prolonged period of time.
- In unconscious and trauma patient's drug can be administered.
- Drugs bypass first pass metabolism so increases bioavailability.
- Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
- Drug absorption by the passive diffusion.
- Flexibility in physical state, shape, size and surface.
- Maximized absorption rate due to close contact with the absorbing membrane.
- Rapid onset of action.

LIMITATIONS OF BUCCOADHESIVE DRUG DELIVERY [19]

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
- Drug required with small dose can only be administered.
- Those drugs which are absorbed by passive diffusion can only be administered by this route.
- Eating and drinking may become restricted.

APPLICATION OF MUCOADHESIVE BUCCAL FILM IN ORAL MEDICINE

Nicotine replacement therapy (NRT)

The habitual nature of smoking is partly due to nicotine in tobacco, which is categorized as a psychoactive substance. In NRT, the nicotine delivery routes are the skin and mucosal membranes, such as buccal and nasal mucosa, because both the neutral and protonated forms of nicotine can readily permeate across the mucosal membranes [20]. Pongjanyakul et al. [21] prepared sodium alginate-magnesium aluminum silicate (SA-MAS) buccal films loaded with nicotine as a potential drug delivery system. The study revealed that the nicotine loaded SA-MAS films provided higher nicotine content and slower rate of nicotine across the mucous membrane than the nicotine loaded SA films. Obaidat et al. conducted a study to determine the feasibility of the formulation as a nicotine replacement product to aid in smoking cessation. The results of the study showed that xanthan mucoadhesive buccal patches are potential candidates for controlled biphasic nicotine delivery. These films helps in fast initial drug release followed by a controlled release over a period of 10 hours [22].

Management of oral candidiasis

Systemic antifungals such as fluconazole (100 mg/day for 1 or 2 weeks) are most preferred drugs for management of oral candidiasis. However, this dose of fluconazole could results in notable side effects varying from headache, nausea to liver dysfunction, and hepatic failure. The oral fluconazole may have variety of drug interactions including with oral hypoglycemics, coumarin-type anticoagulants, cyclosporins, terfenadine, theophylline, phenytoin, rifampin, and astemizole. Thus, the systemic side effects of fluconazole can be reduced by increasing its oral concentration in oral fluids rather than systemic absorption. The reported topical efficacy of fluconazole together with the adverse effects and drug interaction of systemic fluconazole justifies the design of mucobuccal drug delivery system containing a small dose of fluconazole to increase the contact between the drug and the pathogenic yeast for a longer period of time [23].

Management of oral pain and inflammation

Inflammatory processes are one of the major reasons for oral cavity diseases such as gingivitis, periodontitis, stomatitis, aphthous ulcerations etc. [24]. This problem is managed with topical administration of various NSAIDs like diclofenac, flurbiprofen, ketorolac, ibuprofen etc. The advantage of using mucobuccal patch containing the drug is the reduction of drug dose, drug localization in the target tissue and consequent less systemic side effects [25]. Perioli et al. designed sustained-release mucoadhesive bilayered tablets, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for topical administration of flurbiprofen (20 mg) in the oral cavity. The study results showed better anti-inflammatory response and sustained release of drug in the buccal cavity for 12 hours and thus a reduction in daily drug dosage to 40 mg as compared to dose 70 mg in systemic treatment [24].

Management of postoperative periodontal pain

NSAID are most commonly prescribed drugs for postoperative periodontal pain. However, they have numerous side effects. As a result, nutraceuticals such as curcumin are widely used for its well-known safety and medicinal values. A split-mouth study was conducted to evaluate the efficacy of a curcumin mucoadhesive film for pain control after periodontal surgery among 15 patients with 30 sites. The study concluded that curcumin mucoadhesive film showed promising results in reducing postoperative pain and swelling over a period of 1 week, hence showing its analgesic effect after periodontal surgeries [26].

Management of herpes

Acyclovir, an antiviral drug is widely used in the management of oral herpetic lesions. Since the permeability of acyclovir is low in oral mucosa, the efficiency of acyclovir is greatly reduced. In a study by Nair et al, acyclovir was incorporated into the polymeric materials and formulated as nanoparticles. The prepared nanoparticles were then loaded into various films (F5-F7) prepared with varying quantities of hydroxyethyl cellulose and Eudragit RL 100. The prepared films were evaluated for physico-mechanical characters (mucoadhesion, swelling), in vitro acyclovir release and ex vivo diffusion. The results of the study showed adequate mucoadhesive strength and excellent physico-mechanical properties. This study concludes that the drug loaded nanoparticles impregnated buccal film could be an alternative approach to enhance the oral bioavailability of acyclovir, and need to be proved in vivo [27].

Management of aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is one of the most common ulcerative diseases of the oral mucosa which is recurrent, painful and slow to heal. Treatment is primarily for pain relief, reduce healing time and the rate of recurrence. A study was conducted to prove the effectiveness of topical buccal bilayer mucoadhesive films containing sodium alginate and gellan gum loaded with low dose of 1 mg prednisolone sodium phosphate in reducing the treatment period and decrease side effects of systemic treatment. The bilayer films were thin, flexible with good water uptake, mucoadhesive and mechanical properties. The results of the study suggested that buccal application of the developed bilayer mucoadhesive films loaded with only 1mg of prednisolone provided mucoadhesive and convenient application and was able to promote RAS healing with shorter treatment duration [28].

Targeted therapy for oral cancer

Targeted therapy is the most desired treatment for oral cancer, aiming for specific site delivery and thereby lowering the side effects and levels of systemic toxicity. The delivery of therapeutics through nanodelivery systems consisting of polymers or lipids have demonstrated increased solubility, stability and bioavailability, accumulating even inside tumor cells. A study was conducted for the development of a mucoadhesive patch of methotrexate (MTX) for targeted delivery in oral cancer. The developed liposomes and liposomes cast in the film formulation were evaluated for cytotoxicity in Haemopoetic stem cells (HSC-3) using an MTT assay, and a significant decrease in the half maximal inhibitory concentration of MTX was identified with the MTX-entrapped liposomal film, M-LP-F7. The results of the mitochondria-dependent intrinsic pathway demonstrated that there was significant mitochondrial membrane potential disruption with M-LP-F7 compared with the plain drug. M-LP-F7 increased the rate of apoptosis in HSC-3 cells by almost 3-fold. Elevated levels of reactive oxygen species provided evidence that M-LP-F7 exerts a pro-oxidant effect in HSC-3 cells [29].

CONCLUSION

A mucoadhesive drug delivery system offers numerous advantages in terms of economy, accessibility, administration, withdrawal and patient compliance. Mucoadhesive dosage forms provide prolonged contact time at the site of attachment, cost effective with high patient compliance. Buccal mucosa is well supplied with both vascular and lymphatic drainage and avoid extensive first pass drug metabolism, allows controlled drug delivery for extended periods of time. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. However, the need for safe and effective buccal permeation is a crucial component for a prospective future in the area of buccal drug delivery. Additionally, these novel mucoadhesive formulations require much more research work to understand how to deliver drug clinically for the treatment of both systemic and topical diseases.

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