ADVANCED BUCCAL FILM TECHNOLOGY IN THE MANAGEMENT OF ORAL MICROBIAL INFECTIONS

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1.0 Introduction:

Buccal films are mucoadhesive oral dosage forms made up of an active ingredient, a hydrophilic polymer, and additional excipients. Films are applied to the buccal mucosa's inner membrane, where they hydrate, adhere, and dissolve the drug after coming into contact with saliva. This can have either local or systemic effects. They are promising substitutes for traditional oral formulations because of their great flexibility, ease of application, accurate dosage, and greater area of drug absorption. They have been demonstrated to enhance drug efficacy and bioavailability, lower dosage and frequency of administration, and lessen the toxicity brought on by traditional drug therapies. They are intended to be oral delivery systems for substances with adverse pharmacokinetic characteristics. [1]

The buccal mucosal lining offers some distinct advantages over oral drug delivery. It is highly vascularized and exhibits reduced enzymatic activity, less sensitivity, ease of administration and expulsion of the dosage form in the event of adverse effects, avoidance of stomach acid hydrolysis, and circumvention of the hepatic first-pass effect. Because it increases the drug's bioavailability, it requires a lower dose and causes fewer dose-related side effects than other administration methods. Furthermore, compared to other non-oral drug delivery methods, buccal administration shows superior patient adherence. Because of the direct access to the jugular vein and the prolonged therapeutic effect, this route is ideal for powerful medications, particularly those intended for acute conditions with quick clinical response. [2-4]

Polymeric matrices loaded with drugs have been employed for the regulated buccal administration of antifungals and antimicrobials. Furthermore, the majority of oral illnesses can be administered locally, eliminating the need for drug ingestion and systemic distribution. Formulations that extend the duration of medication release in the mouth provide significant benefits for both preventing and treating local illnesses. It is possible to apply sustained or controlled-release medication to the buccal mucosa delivery method that could sustain a consistent drug release.[5]

The short residence time at the site of application is one specific issue that many drug delivery systems share when treating oral cavity diseases. Since an efficient buccal release system should be flexible and bio adhesive by nature to ensure drugs/therapeutics stay in the oral cavity for a desired period of time, the use of bio adhesive polymers as delivery vehicles has garnered significant attention in recent years as a solution to this issue.[6]

Dental decay, gum and periodontal diseases, and oral cancer are among the common pathologies of the oral cavity; oral squamous cell carcinoma (OSCC) accounts for over 80–90% of all oral cavity neoplasms. [7,8]

Different infectious pathogens and modifiable risk factors, such as poor hygiene, sugar consumption, tobacco use, alcohol consumption, and other harmful habits, are the causes of oral diseases; their impact is influenced by a number of social and commercial factors. Many oral health issues could be prevented or treated in their early stages, according to a World Health Organization (WHO) resolution. [9-11]

Antimicrobial resistance is influenced by a variety of factors, but the misuse of antibiotics and the lack of effective antibiotics on the market are the main causes of the global spread of antibiotic-resistant bacteria.[12]

In order to prevent the spread of antimicrobial-resistant pathogens, this crisis necessitates international cooperation and a thorough effort to develop and manufacture efficient antimicrobial agents.[13]

2.0 Novel Buccal Dosage Form:

The buccal dosage forms of the novel type include buccal adhesive films, tablets, patches, and semisolids (ointments and gels), powder [14]. Tablets for buccal mucoadhesive are dry. Dosage forms, which become moist when come into contact with the buccal mucosa [15]. For instance, a double-layer tablet made up of HPC's adhesive matrix layer and polyacrylic acid with a cocoa core inside insulin-containing butter and a penetration enhancer.[16]

2.1 Buccal patch and film:

Buccal patches are made of two laminates, with an aqueous solution of the adhesive polymer cast on a consistent, permeable backing sheet that is then cut into the desired shape [17]. Zi lactins a novel mucosal adhesive film made from an alcoholic solution of HPC and three organic acids. Even when challenged, the film applied to the oral mucosa can stay in place for at least 12 hours.[18]

2.2 Semisolid preparation (Ointments and gels)

Solid bio adhesive dosage forms are more patient-friendly than bio adhesive gels or ointments, and the majority of these dosage forms are only utilized for oral cavity local therapy.[19] "Oral base," one of the first oral mucoadhesive delivery systems, is made up of finely ground pectin, gelatin, and Na CMC distributed in a minute. [20]

2.3 Powders:

Powdered beclomethasone and HPC form when applied to the oral mucosa of rats, a notable rise in the number of times in relation to an oral solution is observed, and 2.5% of beclomethasone is kept on buccal mucosa for more than four hours [21]. Taste, irritation, allergies, and unfavorable characteristics like tooth erosion or discoloration can restrict the list of potential medications for buccal path. A mucoadhesive might be present in the film.

Layer of polymer that attaches to the oral Drug properties can draw a line for using the oral cavity as a location for medication administration. The patch is taken off from the mouth and eliminated following a designated time [22].

3.0 Materials and methods:

The primary film-former was starch (0.50 g), and to increase flexibility and muco adhesion, HPMC E15 (0.10 g) was added. The medication (0.10 g) was the active ingredient, and

glycerol (0.15 g) was the plasticizer. A 50 mL casting solution was prepared using water as the solvent. After heating the starch with water until it gelatinized, it was allowed to cool somewhat. Glycerol, the medication, and HPMC were added one after the other while being constantly stirred. To achieve homogeneous films, the mixture was completely mixed, degassed to eliminate air bubbles, cast onto a level surface, and dried at 40–45 °C or room temperature.

4.0 Composition of buccal film:

The following characteristics must be present in the oral films' active ingredients: The standard drug must be taken in tiny doses.[23]

i. Controlled drug dosage is an excellent option for medications having a biological half-life of two to eight hours. Oral delivery results in larger values or more variations in the drug's maximum dosage.

ii. Plasticizer: The plasticizer has a significant impact on the mechanical characteristics of films. mechanical characteristics of films, like elongation and tensile strength. These characteristics are impacted by variations in plasticizer content. The plasticizer makes the membrane more flexible and less brittle.[23]

iii. Mucoadhesive polymers: Depending on the formulation type, polymers with various characteristics must be taken into account.[24]

iv. Sweeteners: In the oral integrated medication delivery system, sweeteners are becoming crucial excipients. Children are especially sensitive to the preparation's sweet flavor. Both artificial and natural sweeteners are used to enhance the flavor of oral treatments.[24]

v. An agent that stimulates saliva: Increasing the rate of saliva secretion by the use of chemicals that promote saliva production is intended to facilitate the quicker integration of rapidly dissolving film preparations. Acids are generally utilized as salivary stimulants in food preparation.[25]

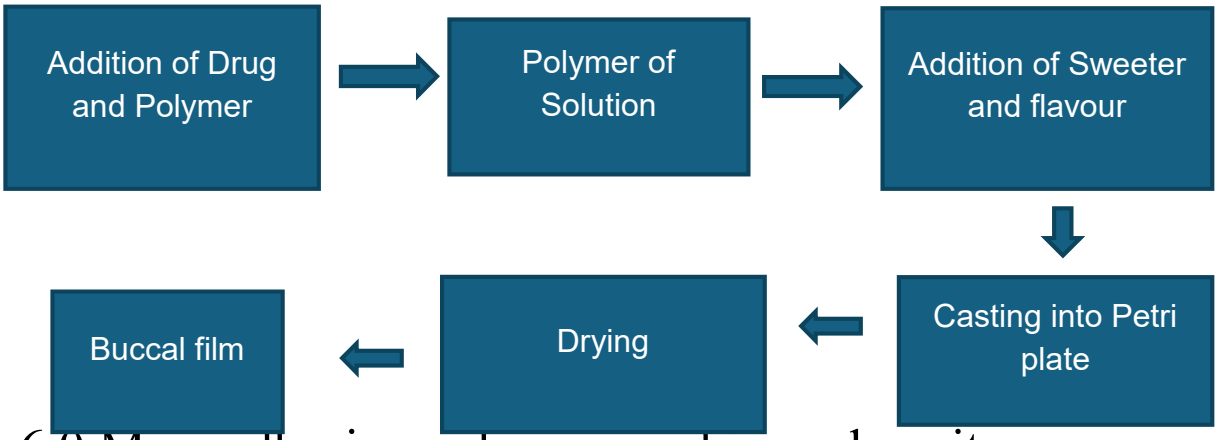
vi. Flavoring agent: Another material known as a flavoring agent may be present in an oral dispersible system. [26]

S. No	COMPOSITION OF FILM	QUANTITY%
1.	Active pharmaceutical agent	1-25
2.	Film forming polymer	40-50
3.	Plasticizer	0-20

4.	Saliva stimulating agent	2-6
5.	Sweetening agent	3-6
6.	Flavouring agent	10
7.	Colouring agent	1

5.0 Preparation of buccal film:

Aluminum foil cups placed on a glass surface were utilized as the substrate for the solvent casting process used to create buccal films of chlorhexidine [27]. HPMC-E15 Propylene glycol, a plasticizer, was used in a 30% w/w concentration. The predicted amounts of polymers were dispersed in ethanol, which served as the solvent. After pulverization with 30% w/w propylene glycol, three hundred mg of chlorhexidine were added to the polymeric solutions to act as a plasticizer and penetration enhancer. To achieve clear, bubble-free gels, the medicated gels were left at room temperature for the whole night. Medicated gels were put into the vials and securely sealed with rubber closures to stop the alcohol from evaporating. To create a flexible film, the gels were cast into 4.5 cm-diameter aluminum foil cups, set on a glass surface, and let to cure overnight at ambient temperature (25°). Before being used again, the dried films were cut into 20 mm diameter pieces, wrapped in aluminum foil, and kept in a desiccator.[28]



6.0 Mucoadhesive polymer used in oral cavity:

Muco adhesion is primarily caused by polymer hydration and swelling due to water diffusion and subsequent mucin dehydration. Swelling should strengthen the mucoadhesive strength by encouraging polymer chain flexibility and mucin chain interpenetration. The polymer to be utilized for buccal formulation is determined by its degree of spread ability and capacity to create distinct kinds of intermolecular linkages at different hydration stages. The methods of adhesion between the polymer and mucin are explained by a variety of theories, including wetting, diffusion, fracturing, adsorption, electrical and dehydration. Wetting theory states

that the muco adhesion between the surfaces can be explained by the spreading coefficient and work of adhesion.[28]

Quantitative assessment of a material's wetting using contact angle using wetting theory, a goniometer can measure muco adhesion. According to fracture theory, the mucoadhesive strength is determined by the force needed to separate the mucosal membrane from the contact surface.[29]

The adhesive force between the two contact surfaces is usually measured using a texture analyzer and modified balance.[30] According to diffusion theory, the penetration rate and depth are determined by a concentration gradient-driven diffusion process involving mucoadhesive polymer and mucin.[31] Numerous variables, including molecular mass, viscosity, elasticity, crosslinking density, hydrogen bonding capacity, charge, solubility, hydration, swelling, and contact time, affect the polymer's diffusion coefficient.[32]

Diffusion-based interlocking between the polymeric platform and the mucus glycoprotein chain could be assessed by measuring the degree of hydration and swelling index. Electronic theory states that an electric double layer and subsequent muco adhesion result from electron transfer caused by attraction between oppositely charged surfaces [33]. Muco adhesion is explained by the adsorption theory as a physicochemical interaction between the contacting surfaces due to weak secondary intermolecular interactions or strong primary bonds.

The mucoadhesive qualities of catechol-cross linked chitosan and mucin were assessed. Surface plasmon resonance spectroscopy analysis of the residual amount of catechol-tethered chitosan showed approximately 10 hours of in vivo retention and a four-fold increase in muco adhesion when compared to unmodified chitosan and chitosan with poly (acrylic acid) following oral administration. The analysis unequivocally shown that conjugating polymers with catechol groups can enhance their intrinsic mucoadhesive properties.[34]

A recent study examined the muco adhesion to hydrated buccal tissue and the efficient buccal administration of dexamethasone loaded in poly (lactic-co-glycolic acid) (PLGA) nanoparticles using a mussel-inspired mucoadhesive buccal film made from PVA-DOPA. [35]

7.0 Rationalist approaches:

7.1 Cardiovascular disease

One of the main cardiovascular conditions, hypertension, requires lifelong treatment to stay under control. The majority of antihypertensive medications, include isosorbide mononitrate, carvedilol, metoprolol, and propranolol. A lower effective dose of carvedilol, a model antihypertensive medication, is reportedly 3.125 mg, however the recommended dosage is 0.025 g twice daily. Therefore, a lesser dosage of medication can successfully deliver the typical dose effect by extending the contact period and avoiding first pass metabolism. Once

more, by maintaining the medication release, frequent drug administration can be avoided, improving patient compliance [35-37]

7.2 A migraine

It is believed that migraines are caused by the dilatation of specific blood arteries in the brain. The "triptan" class of medications, which includes sumatriptan, zolmitriptan, and rizatriptan, is used to treat the condition. Both the nasal and subcutaneous routes have drawbacks, such as the nasal solution's shorter retention period and the injectables' incapacity to self-administer [38-39].

7.3 Vomiting and nausea

Ondansetron HCl, which was selected as a model medication to treat postoperative nausea and vomiting related to emetogenic cancer treatment, has two qualities that a medication should have in order to be absorbed through the buccal mucosa: low molecular weight and biphasic solubility. Because of its low dose (4–8 mg) and 50%–60% absorption when taken orally, it can be easily put onto a patch [40-42].

8.0 Therapeutic approach:

8.1 Anti-inflammatory medication

One of the main causes of diseases of the oral cavity is inflammatory processes [43]. Gingivitis, periodontitis, stomatitis, oral ulcers, and other oral cavity pathologies are treated with topical administration of different nonsteroidal anti-inflammatory medications. They have the advantage of lowering the dosage, minimizing the severity of systemic side effects due to the drug's localization in the target tissue [44-46]

8.2 Antimicrobial therapy

Films of chlorhexidine for topical treatment of oral disease in order to minimize side effects and potential drug interactions during systemic therapy, as well as to guarantee a satisfactory drug level in the mouth for an extended period of time [47]. In an effort to treat a variety of oral dental infections, mucoadhesive sodium fluoride was created [46]. Chitosan-based buccal films were created using chlorhexidine diacetate [48]. For possible use as an antimicrobial agent to treat oral infections, complexes containing starch and HPC were prepared and added to a mucoadhesive [49]. A palatal mucoadhesive buccal film containing a formulation [50-51] was created in an effort to eliminate oral.

HPMC, starch, and glycerol were used as the gel-forming ingredients to create a novel mucoadhesive gel of chlorhexidine [52].

9.0 Drug absorption pathway:

9.1 Enzymatic breakdown and salivary washout

Proteases, esterases, and amylases found in saliva and mucosal tissues quickly break down peptide-based and labile drugs, especially large biopharmaceuticals.[53-55]Protein-based agents may lose up to 90% of their activity within 30 minutes of exposure, highlighting their instability.[56] Mucoadhesive polymers like chitosan and carbopol increase contact time but exhibit inconsistent adhesion influenced by patient-specific factors.[57] Nanocarriers, such as liposomes, improve mucosal penetration, achieving up to 3.2-fold increased delivery with over 80% protection. [58]-fold increased delivery with over 80% protection. By releasing medications in reaction to physiological stimuli, stimuli-responsive hydrogels improve targeting even more. For instance, pH-sensitive nanospheres released 80% of metronidazole at pH 6.5 as opposed to less than 50% at pH 7.4.31 Despite these developments, formulation instability, scaling problems, and a lack of long-term safety evidence continue to hinder clinical translation. [59-60]

9.2 Limitations of mucosal permeability

The oral mucosa exhibits region-specific permeability; non-keratinized areas, like the buccal, sublingual, and ventral tongue mucosa, are ideal for drug transport due to their rich vascularity, thin epithelium (100–200 μm), and increased permeability. Tight intercellular junctions, a dense mucin coat (50–500 μm), and stratified squamous epithelium (15–30 layers) form a strong barrier for hydrophilic molecules and macromolecules like peptides, proteins, and nucleic acids, which frequently exhibit absorption rates below 5–10%. [61]

Because of their thicker epithelium (up to 500 μm) and compact lipid architecture, keratinized areas like the gingiva and hard palate offer mechanical resilience but have two to five times lower permeability. [62] This heterogeneity calls for careful site selection and sensible delivery system design. By temporarily loosening tight connections or avoiding

mucus, advanced techniques like penetration enhancers, chitosan-modified nanoparticles, and muco-penetrating carriers significantly increase drug flow and therapeutic efficacy. [63-65]

10.0 EVALUATION TEST:

10.1 Minimum Bactericidal Concentration

The wells displaying the bacteria inhibited by the previously described broth microdilution method were subsequently plated on Mueller Hinton agar (MHA) and fungal inhibition on Dextrose Agar, and they were cultivated at 370 degrees for 20 hours. The lowest drug concentration that killed 99.9% of bacteria or fungi and prevented any growth on plates was known as the Minimum Bactericidal Concentration (MBC).

10.2 Time-killness kinetics

Escherichia coli ATCC 25922, Candida albicans ATCC 10231, Pseudomonas aeruginosa ATCC 27853, and Staphylococcus aureus ATCC 25923 were sub cultured then dilute to 0.5 McFarland standard. The test tubes were incubated at 37°C with an inoculum size 1.0 × 106 cfu /mL of standardized organisms. At intervals of 0, 6, 12, 18, 24, and 30 hours for bacteria and 0, 6, 12, 30, 36, 48, 54, and 72 hours for fungi, aliquots (1.0 mL) of the medium were taken and aseptically inoculated to nutrient agar in the sterile Petri dish. The Petri dishes containing the inoculum were incubated at 37°C for 24 hours after the agar was allowed to set. The organisms alone were the subject of a control test. The process was carried out in triplicate, and the test organisms' colony-forming unit (CFU) was ascertained. A log CFU/mL versus time graph was created. GraphPad Prism Version 5.10 for Windows (GraphPad Software Inc., San Diego, USA). SA was used to analyze the study's data using one-way ANOVA and Dunnett's post hoc test.

10.3 In vitro mucoadesive strength

This study used freshly cut goat buccal mucosa as a model to measure the film's muco adhesion strength. A piece of buccal mucosa was stored at 4°C for two hours in Krebs buffer to prevent it from going bad. Before being used again, the goat mucosa came to room temperature. Films stuck to the Santam instrument's upper lever, while a few drops of PBS (pH 6.8) stuck goat mucosa to the fixed lever. The film spent a minute in contact with the

mucosa. The movable lever then rose at a rate of 2 mm/min. The mucoadhesive strength of the film was determined by calculating the force needed to rupture the mucosal surface.[66]

11.0 Factors affecting drug absorption:

Drug delivery is complicated in the oral cavity because there are numerous independent and connected factors which lowers the concentration that can be absorbed at the location of absorption [67].

11.1. Membrane Factors:

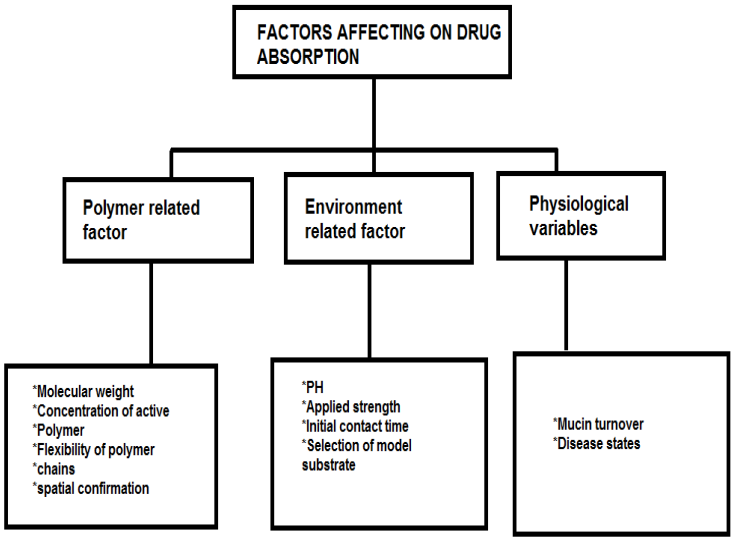
This includes the extent of keratinization, mucus, and surface area of absorption salivary pellicle layer, intercellular lipids in the epithelium, lamina propria and basement membrane. Furthermore, the thickness of the absorptive membrane, blood flow, and lymph. Enzyme content, cell renewal, and drainage will all help lower the quantity and rate of drug entry the circulation throughout the body.

11.2. Environmental Elements:

a. Saliva: A thin layer of saliva covers the entire salivary lining of the buccal mucosa film or pellicle. Salivary film thickness is 0.07. up to 0.10 mm. The composition, thickness, and this film's movement influences the buccal absorption.

b. Salivary glands: The smaller salivary glands are situated in the deep or epithelial area of buccal mucosa. They continuously release mucus on buccal mucosa's surface. However, mucus aids in keep mucoadhesive dosage forms, it may obstacle to the absorption of drugs.

c. Buccal tissue movement: The mouth's buccal region. There is less movement in the cavity. The mucoadhesive polymers are essential for Keep the dosage form in the buccal region for prolonged periods of time. To allow tissue movements during speech, and if conceivable when eating or swallowing.



12.0 ADVANTAGES:

i. Chewing and swallowing are not necessary.

ii. Quick onset of action and minimal side effects consequences.

iii. Precise dosage in contrast to liquid form of dosage.

iv. Administration simplicity for children, elderly individuals.

v. Extends the duration of the dosage's residence at the site at the absorption site. Thus, it gets better the drug's bioavailability.

vi. The drug can be shielded from deterioration in an acidic environment and the GI tract. The large surface area of buccal film causes quick disintegration and dissolution within the mouth [68]

vii. Antimicrobial peptides have broad spectrum of antimicrobial activities (antibacterial, antiviral, and antifungal) and a promising class of drugs to face the development of the MDR pathogens. They have benefits over conventional antibiotics or antifungals, which include lesser emergence of resistance, antibiofilm activities and an ability to modulate the host immune response. AMPs are minimum immunogenic than recombinant proteins and antibodies. Also, they are in general considered to have safety profile because have metabolites are natural amino acids and they have short half-life; some peptides accumulated in tissue.[69]

13.0 DRAWBACKS:

Despite these advantages, AMPs have certain drawbacks, include;

i. a short half-life due to rapid degradation by proteolytic enzymes in the bloodstream and gastrointestinal system;

ii. plasma protein binding, which results in their inactivation;

iii. low metabolic stability and low oral bioavailability;

iv. rapid excretion through the kidneys and liver;

v. high toxicity (i.e., nephrotoxicity) and immunogenicity;

vi. a poor correlation between in vitro antimicrobial activity and their effectiveness in vivo; and

vii. high production costs.[70]

Saliva is constantly released into the oral cavity diluting medications at the location of absorption leading to low drug concentrations on the surface of the absorbing membranes Saliva is instinctively swallowed, which causes a maximum portion of the dissolved or

Removal of suspended released drugs from the absorption site. unfavorable characteristics like Tooth erosion or discoloration can restrict the list of potential medications for buccal route. Traditional buccal medication Delivery networks prevented the patient to concurrently consume food, liquids, or some while conversing. [71-73]

14.0 PACKAGING:

There are numerous ways to package buccal films, including single pouch, blister card with continuous roller dispensers, numerous units, and multiple-unit dispensers. A single container is essential for movies. The most popular packing system is an aluminum pouch. For oral films, there are some patented packing solutions. The firm Labtec has a patent Amcor Flexibilities Company has patented a packaging method known as Rapid card. Core-peel technique [74]

15.0 APPLICATION OF BUCCAL FILM:

15.1 Controlled and sustained release

For long-term release, hospitals use buccal films. preparations, as well as various polymer excipients like derivatives of chitosan because they aid in wound healing dressings, lessen toxicity, and have potent water adhesive qualities and resistance. [75]

15.2 Nicotine replacement therapy

Nicotine is a psychoactive ingredient found in tobacco. increases the addictive nature of smoking. Because it's simple to entry through the mucosal barrier, the mucosal technique. In this therapy, delivery is the most successful approach.[76]

15.3 Antifungal infection

A systemic antifungal medication is used to treat oral candidiasis. One common option for mucosal delivery is fluconazole. It's can lessen its detrimental systemic effects by enhancing its oral concentration. For an extended period, Pathogenic yeast and medication have both

increased in frequency. contact, using low dosages of fluconazole through mucoadhesive buccal films, which eventually raised its efficiency.

15.4 Asthma

It is planned to administer sodium cromoglycate.to treat asthma using buccal film. The drug must be created with a controlled release mechanism because of its brief half-life. Both of a decrease in the maximum plasma concentration in the blood and an extension of the time required to get there was the results of applying this drug in buccal film. It's offered regulated drug release as well.

15.5 FDA-approved buccal film

One option is to use muco adhesive buccal films. substances strong enough to fulfill the prerequisites for buccal film administration are used. Four buccal films have been approved by the USFDA [77-78].

16.0 CONCLUSION:

Mucoadhesive buccal films are a novel, patient-friendly method of directly administering antibacterial and antifungal medications to the mouth cavity. The formulation of HPMC, starch, glycerol, and a few antibacterial medications in this review shows how basic polymeric systems can be used to accomplish successful local therapy. While starch improves mechanical strength and stability, HPMC serves as the main mucoadhesive and film-forming polymer. Glycerol is added to create smooth, easily applied films by preventing brittleness and adding flexibility. Together, these elements provide better therapeutic efficacy against oral infections, regulated release, and extended retention at the application site. Buccal films provide a longer residence period, less frequent dosing, and fewer systemic adverse effects than traditional dose forms.

All things considered, the combination of these excipients offers a dependable, affordable, and effective platform for antibacterial and antifungal treatment, underscoring the increasing significance of mucoadhesive buccal films in modern oral drug administration.

REFERENCE:

1. Salehi, S.; Boddohi, S. New formulation and approach for mucoadhesive buccal film of rizatriptan benzoate. Prog. Biomater. 2017, 6, 175–187.

2. Gilhotra, R.M.; Ikram, M.; Srivastava, S.; Gilhotra, N. A clinical perspective on mucoadhesive buccal drug delivery systems. J. Biomed. Res. 2014, 28, 81–97.

3. Macedo, A.S.; Castro, P.M.; Roque, L.; Thomé, N.G.; Reis, C.P.; Pintado, M.E.; Fonte, P. Novel and revisited approaches in nanoparticle systems for buccal drug delivery. J. Control Release 2020, 320, 125–141.

4. Birudaraj, R.; Mahalingam, R.; Li, X.; Jasti, B.R. Advances in buccal drug delivery. Crit. Rev. Ther. Drug Carr. Syst. 2005, 22, 295–330.

5. Scholz OA, Wolff A, et al. "Drug delivery from the oral cavity: focus on a novel mechatronic delivery device", Drug Discovery Today, 2008, 13(5-6):247–253.

6. Asati, Jain, and Choubey 2019; Alawdi and Solanki 2021; Fonseca-Santos and Chorilli 2018).

7. Pires, F.R.; Ramos, A.B.; de Oliveira, J.B.C.; Tavares, A.S.; de Luz, P.S.R.; dos Santos, T.C.R.B. Oral squamous cell carcinoma: Clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. J. Appl. Oral Sci. 2013, 21, 460–467.

8. Sathish, N.; Wang, X.; Yuan, Y. Human Papillomavirus (HPV)-associated Oral Cancers and Treatment Strategies. J. Dent. Res. 2014, 93, 29–36.

9.Di Stefano, M.; Polizzi, A.; Santonocito, S.; Romano, A.; Lombardi, T.; Isola, G. Impact of Oral Microbiome in Periodontal Health and Periodontitis: A Critical Review on Prevention and Treatment. Int. J. Mol. Sci. 2022, 23, 5142.

10. Zhang, Y.; He, J.; He, B.; Huang, R.; Li, M. Effect of tobacco on periodontal disease and oral cancer. Tob. Induc. Dis. 2019, 17, 40.

11. Lamster, I.B. The 2021 WHO Resolution on Oral Health. Int. Dent. J. 2021, 71, 279–280.

12. Alanis, A.J. Resistance to antibiotics: Are we in the post-antibiotic era Arch. Med. Res. 2005, 36, 697–705.

13. Hlth, N.C.E.; Stat, N.C.H. Control of infectious diseases, 1900–1999. JAMA J. Am. Med. Assoc. 1999, 282, 1029–1032, reprinted in MMWR 1999, 48, 621–629.SSSSS

14. Jain NK. Controlled and Novel Drug Delivery, 1st edition, published by CBS Publishers and Distributors, New Delhi. 1997; 52-81.

15. Patel KV, Patel ND, Dodiya HD, Shelat PK. Buccal bio adhesive drug delivery system: an overview. Ind. J. of Pharma. & Bio. Arch.2011; 2(2): 600-609.

16. Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system Ind. J .Pharm. Sci. Res. 2011; 2(6): 1303-1321.

17. Gandhi BR, and Robinson JR. (1988). Bio adhesion in drug delivery .Ind. J. Pharm. Sci. 1988; 50:145−152.

18.Boddupalli BM, Mohammad ZNK, Nath RA, Banji D.muco adhesive drug delivery system an overview. J. Adv. Pharm .Tech. Res. 2010; 1(4): 381-387.

19. Nazila SM, Montakar C, Thomas PJ. The use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews. 2005; 57:1666– 1691.

20. Tangri P,Sateesh Madhav NV.Oral mucoadhesive drug delivery system. Int J of biopharmaceutics 2011;2(1):36-46

21. Ragvendra NG, Shravani B, Reddy MS.Overview on buccal drug delivery systems.Journal of pharmaceutical science andresearch.2013;5(4):80-88

22. Mishra S, Kumar G,Kothiyal P. A review article: Recent advances in buccal patches.2012;1(7):78-86.www.thepharmajournal.com (1):41-53.

23. Sindu G.D., Lavanya Nallaguntla, and Gururaj S.Kulkarni Buccal mucoadhesive film. Int J Currpharm res, 2021; 13(4): 14-20.

24. Radha Madhavi B., Varansi SN Murthy, Prameela Rani A., and Dileep Kumar Gattu; Bucal film drug delivery systems: an innovative and emerging technology; molecular pharmaceutics and organic process research, 2013; 1(3): 2–6.

25. Pandya Ketul*, K.R. Patel, M.R. Patel, N.M. Patel. Fast Dissolving Films: A Novel Approach to Oral Drugs Delivery. IJPTP, 2013; 4(2): 655–661.

26. Muhammad Hanif, Muhammad Zaman, and Vesh Chaurasiya; polymer used in buccal film; A review; designed monomer and polymer, 2015; 18(2): 105-111.

27. 22.Devi K, Paranjothy KL. Development and evaluation of free film and transdermal patches of ketorolac tromethamine using polymers and pressure sensitive adhesives. East Pharma. 1998;485:97

28. Hombach, J.; Bernkop-Schnürch, A. Mucoadhesive drug delivery systems. Handb. Exp. Pharmacol. 2010, 197, 251–266.

29. Chang, R.-J.; Gent, A.N. Effect of interfacial bonding on the strength of adhesion of elastomers. I. Self-adhesion. J. Polym. Sci. Polym. Phys. Ed. 1981, 19, 1619–1633

30. Smart, J.D. Buccal drug delivery. Expert Opin. Drug Deliv. 2005, 2, 507–517.

31. Yang, C.; Xing, X.; Li, Z.; Zhang, S. A Comprehensive review on water diffusion in polymers focusing on the polymer-metal interface combination. Polymers 2020, 12, 138.

32. Karoyo, A.H.; Wilson, L.D. A review on the design and hydration properties of natural polymer-based hydrogels. Materials 2021, 14, 1095

33. Shinkar, D.M.; Dhake, A.S.; Setty, C.M. Drug delivery from the oral cavity: A focus on mucoadhesive buccal drug delivery systems. PDA J. Pharm. Sci. Technol

34. Kim, K.; Kim, K.; Ryu, J.H.; Lee, H. Chitosan-catechol: A polymer with long-lasting mucoadhesive properties. Biomaterials 2015, 52, 161–170.

35. Hu, S.; Pei, X.; Duan, L.; Zhu, Z.; Liu, Y.; Chen, J.; Chen, T.; Ji, P.; Wan, Q.; Wang, J. A mussel-inspired film for adhesion to wet buccal tissue and efficient buccal drug delivery. Nat. Commun. 2021, 12, 1689

36.Thimmasetty J, Pandey Gs, Sathesh Babu Pr. Design and In Vivo evaluation of carvedilol buccal mucoadhesive patches. Pak. J. Pharm. Sci. 2008;21:241–48.

37.Naveen C, Kumar YK, Rao PV, Rao TR. Chemical enhancers in buccal and sublingual delivery. Int J Pharm Sci Nanotech. 2011;4:1307–19.

38.Medline Plus A. service of the U.S National Library of Medicine and the National Institutes of Health. Available at: http://medlineplus.gov. 2008.

39.Dechant KL, Clissold SP. Sumatriptan, A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs. 1992;43:776–98.

40.Shayeda Dharani S. Formulation and in vitro evaluation of mucoadhesive buccal patches of ondansetron hydrochloride. Int J Pharm Sci Nanotech. 2010;3:860–6.

41.Lachaine J, Laurier C, Langleben A, Vaillant L. Cost-effectiveness and quality of life evaluation of ondansetron and metoclopramide for moderately emetogenic chemotherapy regimens in breast cancer. J Oncol Hema. 1999;32:105–12. doi: 10.1016/s1040-8428(99)00025-6. [DOI] [PubMed] [Google Scholar]

42. 56.Perioli L, Ambrogi V, Giovagnoli S, Ricci M, Blasi P, Rossi C. Mucoadhesive Bilayered Tablets for Buccal Sustained Release of Flurbiprofen. AAPS PharmSciTech. 2007;28:E20–E27.

43.Roszkowski MT, Swift JQ, Hargreaves KM. Effect of NSAID administration on tissue levels of immunoreactive prostaglandin E2, leukotriene B4, and (S)-flurbiprofen following extraction of impacted third molars. Pain. 1997;73:339–45

44.Heasman PA, Offenbacher S, Collins J, Edwards GG, Seymour RA. Flurbiprofen in the prevention and treatment of experimental gingivitis. J Clin Periodontol. 1993;20:732–38.

45.Mura P, Corti G, Cirri M, Maestrelli F, Mennini N, Bragagni M. Development of mucoadhesive films for buccal administration of flufenamic acid: Effect of cyclodextrin complexation. J Pharma Sci. 2010;99:3019–29.

46.Ali J, Khar R, Ahuja A, Kalra R. Buccoadhesive erodible disk for treatment of oro-dental infections: design and characterization. Int J Pharm. 2002;238:93–103. doi: 10.1016/s0378-5173(02)00059-5.

47. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug loaded chitosan microspheres. Eur J Pharm Biopharm. 2002;53:233–9. doi: 10.1016/s0939-6411(01)00237-5.

48.Mizrahi B, Domb AJ. Mucoadhesive tablet releasing iodine for treating oral infections. J Pharm Sci. 2007;96:3144–50. doi: 10.1002/jps.20876.

49.Sterer N, Nuas S, Mizrahi B, Goldenberg C, Weiss EI, Domb A, Davidi MP. Oral malodor reduction by a palatal mucoadhesive tablet containing herbal formulation. J Dentistry. 2008;36:535–9. doi: 10.1016/j.jdent.2008.04.001.

50.Hammer KA, Carson CF, Riley TV. Antimicrobial activity of essential oils and other plant extracts. J Applied Micro bio. 1999;86:985–90. doi: 10.1046/j.1365-2672.1999.00780.x.

51.Cavanagh HM, Wilkinson JM. Biological activities of lavender essential oil. Phytotherapy Res. 2002;16:301–8. doi: 10.1002/ptr.1103.

52. Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. Deliv. 2015;6(5):595–608. https://doi.org/10.4155/tde.15.5.

53.Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery system for biopharmaceuticals 2019;11(3):1–20. https://doi.org/10.3390/pharmaceutics11030129.

54.Truong-Le V, Lovalenti PM, Abdul-Fattah AM. Stabilization challenges and formulation strategies associated with oral biologic drug delivery systems. Drug Deliv. Rev. 2015;93:95–108. https://doi.org/10.1016/j.addr.2015.08.001

55.Kumar R, Islam T, Nurunnabi M. Mucoadhesive carriers for oral drug delivery. Control. Release. 2022; 351:504–559. https://doi.org/10.1016/j.jconrel.2022.09.024

56.Asane GS, Nirmal SA, Rasal KB, et al. Polymers for mucoadhesive drug delivery system: a current status. Drug Dev. Ind. Pharm. 2008;34(11):1246–1266. https://doi.org/10.1080/03639040802026012

57.Rahma MN, Suhandi C, Mohammed AFA, et al. The role and advancement of liposomes for oral diseases therapy. J. Nanomedicine. 2025; 20:1865–1880. https://doi.org/10.2147/IJN.S492353.

58.Vergara D, Sanhueza C, Mendez S, et al. Evaluation of preclinical efficacy of curcumin-loaded bicosome systems in amelioration of oral mucositis. 2025;17(2):1–15. https://doi.org/10.3390/pharmaceutics17020181

59.Ezike TC, Okpala US, Onoja UL, et al. Advances in drug delivery systems, challenges and future directions. 2023;9(6):e17488. https://doi.org/10.1016/j.heliyon.2023.e17488

60. Paderni C, Compilato D, Giannola LI, et al. Oral local drug delivery and new perspectives in oral drug formulation. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2012;114(3):e25–34. https://doi.org/10.1016/j.oooo.2012.02.016

61.Liang J, Peng X, Zhou X, et al. Emerging applications of drug delivery systems in oral infectious diseases prevention and treatment. 2020;25(3):1–16. https://doi.org/10.3390/molecules25030516

62.Dubashynskaya NV, Petrova VA, Skorik YA. Biopolymer drug delivery systems for oromucosal application: recent trends in pharmaceutical R&D. J. Mol. Sci. 2024;25(10):1–20. https://doi.org/10.3390/ijms25105359

63.Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. Deliv. 2015;6(5):595–608. https://doi.org/10.4155/tde.15.5

64.Zheng B, Liu D, Qin X, et al. Mucoadhesive-to-mucopenetrating nanoparticles for mucosal drug delivery: a mini review. J. Nanomedicine. 2025; 20:2241–2252. https://doi.org/10.2147/IJN.S505427

65. Qin J, Chai G, Brewer JM, Lovelace LL, Lebioda L. Fluoride inhibition of enolase: crystal structure and thermodynamics. Biochemistry. 2006; 45:793–800

66. Amir H, et al, Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology, 2001, 1-27. 4.

67. Radha MB, Murthy VS. Buccal film drug delivery system-an innovative and emerging Technology. Molecular Pharmaceutics and Organic Process Research. 2013; 1(3):1-6

68. Magana M, Pushpanathan M, Santos AL, Leanse L, Fernandez M, Ioannidis A, et al. The value of antimicrobial peptides in the age of resistance. Lancet Infect Dis. (2020) 20:e216–30. doi: 10.1016/S1473-3099(20)30327-3

69. Divyashree M, Mani MK, Reddy D, Kumavath R, Ghosh P, Azevedo V, et al. Clinical applications of antimicrobial peptides (AMPs): where do we stand now? Protein Pept Lett. (2020) 27:120–34. doi: 10.2174/0929866526666190925152957

70. Mishra S, Kumar G,Kothiyal P. A review article: Recent advances in buccal patches.2012;1(7):78-86.www.thepharmajournal.com

71. Martin-Serrano A, Gomez R, Ortega P, de la Mata FJ. Nanosystems as vehicles for the delivery of antimicrobial peptides (AMPs). Pharmaceutics. (2019) 11:448. doi: 10.3390/pharmaceutics11090448

72. Mahlapuu M, Hakansson J, Ringstad L, Bjorn C. Antimicrobial peptides: an emerging category of therapeutic agents. Front Cell Infect Microbiol. (2016) 6:194. doi: 10.3389/fcimb.2016.001946

73. 32. Pongjanyakul T, Suksri H. Alginate-magnesium aluminum silicate films for buccal delivery of nicotine. Colloids and Surfaces B: Biointerfaces,2009 Nov 1; 74(1): 103-113.

74. Thimmasetty J, Pandey GS, Babu PR. Design and invivo evaluation of carvedilol buccal mucoadhesive patches. Pakistan journal of pharmaceutical sciences, 2008 Jul1; 21(3).

75. 34. Anand V, Kataria M, Kukkar V, Saharan V, and Choudhury PK The latest trends in the taste assessment of pharmaceuticals. Drug Discov Today, 2007; 12: 257–265.

76. Murray OJ, Dang W, Bergstrom D Using an electronic tongue to optimize taste masking in a lyophilized orally disintegrating tablet formulation. Pharm Technol, 2004.

77. Mahajan A., Chhabra N., Aggarwal G. Formulation and characterization of fast-dissolving buccal film. Scholars Research Library, 2011; 3(1): 152-165.

78. Shridhar GS, Manohar SD, Bhanudas SR, Anjaneri N. Mucoadhesive buccal drug delivery: An Overview. Journal of Advanced Pharmacy Education & Research Oct-Dec., 2013; 3(4): 319-2.