

NOVEL FRONTIERS IN BUCCAL PATCHES: A RECENT UPDATE

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ABSTRACT

Buccal route found to be more suitable for the delivery of pharmaceutical agents using mucoadhesive polymers due to presence of relatively static and smooth surface on which various mucoadhesive dosage forms can be placed. Different dosage forms like films, tablets, gels, ointments and patches can be used for delivery of drug across the buccal mucosa. The drugs may be suitable candidates to be delivered via the oral cavity which are having short biological half-life, poor solubility and permeability, susceptible to enzymatic degradation and for achieving sustain release effect. The mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities. The delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora.

Keywords: Buccal patches, Mucoadhesion, Bioavailability, Polymers, NDDS.

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INTRODUCTION

Since from the last 40 years, the concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. The use of various mucoadhesive polymers has achieved the significant interest in formulating the sustained release, extended release as well as prolonged release dosage form.^[1]

For the desired mucoadhesive strength of the mucoadhesive dosage forms, there are various mucoadhesive polymers that can be used. These polymers are either natural or synthetic macromolecules which are capable of adhering to the mucosal surfaces. From last three decades, the use of various mucoadhesive polymers has achieved a great interest in the field of pharmaceutical technology. Nowadays, the use of mucoadhesive polymers has been accepted as an important strategy to prolong the residence time and to improve the localized effects of drug delivery systems on various mucus membranes of a biological system.^[2]

Advantages of buccal adhesive drug delivery system

- The buccal drug delivery provides a relatively rapid onset of action as compare to the other non-oral routes, hence, has a high patient acceptability.
- The buccal mucoadhesive drug delivery system can be used for both local as well as systemic delivery of many drugs.
- Buccal mucoadhesive dosage forms are easy to apply as compare to other adhesive dosage forms.
- It is the most preferred delivery system for the local treatment of drugs. So that there are wide range of mucoadhesive formulations.^[3]
- The drugs, which show poor bioavailability via the oral route, can their bioavailability can be enhanced by formulating their mucoadhesive delivery systems.^{[4] [5] [6]}

Limitations

- The drugs having bitter taste cannot be formulated.
- The drugs which irritate oral mucosa, cause allergic reactions and discoloration of teeth cannot be formulated.
- Sometimes, the degradation of moisture sensitive drugs may take place by saliva.^[7]

Disadvantages of Buccal Drug Delivery System

- Low permeability of the buccal membrane, specifically when compared to the sublingual membrane.
- These are some of the problems that are associated with current buccal drug delivery system.^[8]

General considerations in designing buccal adhesive drug delivery system

Physiological aspects: Due to the constant flow of saliva and regular movement of tissues present in the oral cavity the local delivery of the drugs in oral cavity is the most challenging aspect. Due to the local absorption of drugs, side effects are also being reduced as compared to in case of systemic delivery.^{[9][10]}

Pathological aspects: The barrier property of buccal mucosa is mainly due to the presence of epithelial tissue. The thickness of epithelial tissue can be affected by many diseases that may change the barrier property of epithelial tissue. Some diseases or treatments may cause the alteration in rate of mucus secretion. These changes at the mucosal surface due to various pathological conditions may affect the residence time buccal delivery device.^{[11][12][13]}

Pharmacological aspects: The design and formulation of a buccal delivery dosage form depends upon the nature of delivery (local or

systemic), drug targeting site and mucosal site to be treated. The buccal delivery is generally preferred for systemic delivery as compared to the local delivery of drugs.^[14]

Pharmaceutical aspects: The buccal drug delivery system is generally used for desired absorption of poorly water soluble drugs. For this purpose, firstly, the water solubility of the drug is enhanced by using specific solubility enhancement method e.g., by forming complex with cyclodextrin. Hence by improving solubility, the absorption of drug also get increased in buccal mucosa^[15]. As the buccal mucosa is less permeable, so in order to enhance the permeability, various penetration enhancers can be used. Some commonly used penetration enhancers are bile salts, fatty acids, and sodium lauryl sulphate. Some enzyme inhibitors may be used to inhibiting the degradation of drug by various enzymes present in the saliva due to which the bioavailability of drug can be improved. There are some polymers such as carbopol, polycarophil that can inhibit certain proteolytic enzymes such as trypsin, carbo-peptidases etc.^[16] The buccal mucoadhesive dosage forms can be categorized into three types as given below.

Type I: In this there is a single layer containing dosage form which provides multidirectional drug release. The main disadvantage of this type is that the drug loss is high by swallowing.

Type II: It contains the drug loaded bioadhesive layer covered by impermeable backing membrane. The backing membrane covers only the opposite side from the site of attachment hence preventing the drug loss from the upper surface of device.

Type III: In this type, all sides of drug loaded mucoadhesive layer are covered by impermeable except the side that attaches the target area. It is a unidirectional drug flow preventing all kinds of unwanted drug loss.^[17] The Figure 1 shows various types of buccal dosage forms.

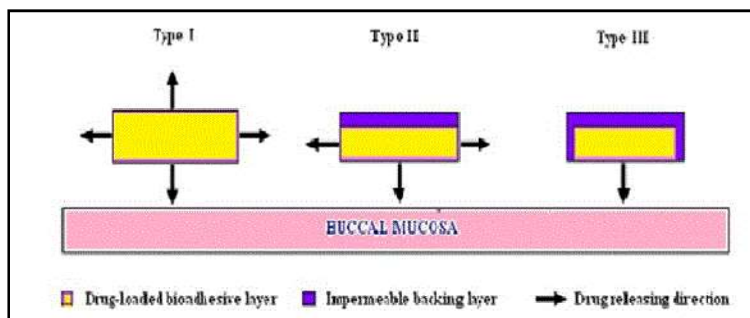


Figure 1: Types of bucco adhesive dosage forms.^[18]

Mechanism of Adhesion

The mucoadhesion can be defined as an interfacial phenomenon in which the two materials, in which one may be artificial such as mucoadhesive polymer and other may be the mucin layer of the

mucosal tissue, are held together by means of interfacial forces of attraction. “Mucoadhesive” is defined as an artificial substance that is capable of interacting with mucus membrane and being retained on them or holding them together for extended or prolonged period of time. During the process of adhesion, generally the two stages

have been identified are given below. These stages of mucoadhesion are also shown in Figure 2.

Contact stage: During this stage, when the mucoadhesive material comes in contact with mucus membrane, an intimate wetting occurs between the mucoadhesive and mucus membrane. This wetting of the mucoadhesive is done by the mucus present in the mucosal membrane.

Consolidation stage: By means of different physicochemical forces of attraction the mucoadhesive material gets joined to the mucus membrane and resulting in a long lasting mucoadhesion.

This is called as the consolidation stage. After these two stages the process of mucoadhesion completes.

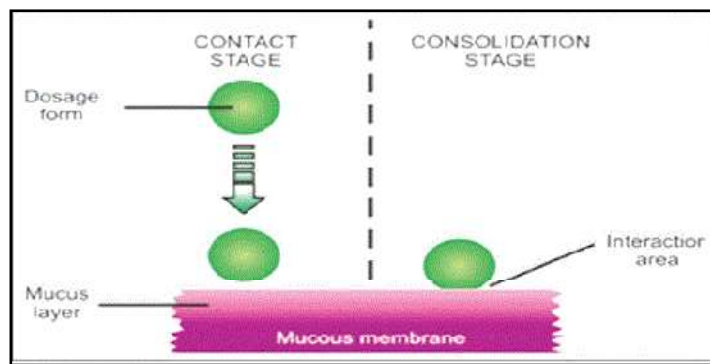


Figure 2: Mechanism of mucoadhesion. [19]

Theories of Adhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they can be either Chemical bond or Mechanical bond. On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated.

Electronic theory

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bioadhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each.

Adsorption theory

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface i.e. mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which is weaker in nature, thus produces a semi-permanent bond. [20]

Wetting theory

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion. [21]

Diffusion interlocking theory

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network.

Fracture theory

The fracture theory is mainly based on the fact that, the force required detaching the polymeric chain from the mucin layer is the strength of their adhesive forces. This strength may be also called as fracture strength. The fracture strength can be determined by using the formula given below

$$G = (E \cdot e/L)^{1/2}$$

Where, G-Fracture strength, E-Young's modulus of electricity, e- Fracture energy, L- Critical crack length.

Factors affecting adhesion

Polymer related factors

Molecular weight: The mucoadhesion strength of a mucoadhesive polymer mainly depends upon its molecular weight and polymeric linearity. Generally, for the linear polymers (e.g., Polyethylene

glycol), the bioadhesive property is directly proportional to the molecular weight

Concentration of polymer: The concentration of a mucoadhesive polymer is a significant factor of determining its mucoadhesive strength. There is an optimum concentration for a mucoadhesive polymer where it produces the maximum mucoadhesion.

Flexibility of polymer chains: Greater the flexibility of the mucoadhesive chain causes the greater diffusion into the mucus network of buccal cavity. This results in increased mucoadhesion. The flexibility of polymer chain decreases with increase in the concentration of polymer. For an effective bioadhesion, the polymer chain should effectively diffuse into the mucus layer. The flexibility of polymer chain depends on the viscosity and diffusion coefficient of that chain.

Spatial confirmation: The mucoadhesive strength of a polymer is also dependent on the conformation or spatial arrangement of polymers i.e., helical or linear. The polymers showing linear conformation having the greater mucoadhesive strength as compare to the polymers showing helical conformation.

Swelling or hydration: The proper hydration of mucoadhesive polymer is essential for the desired mucoadhesive strength. With increase in hydration the pore size of polymer increases which results in induced mobility and enhanced interpenetration.

Hydrogen bonding capacity: Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate and poly (methacrylic acid) as well as all their co-polymers are having good hydrogen bonding capacity [22].

Cross linking density: The cross linking density of the polymer determines its higher molecular weight. The cross linking density indicates the number of average molecular weight of the cross linked polymer, which determines the average pore size. When the cross linking density of polymer is higher, it reduces the pore size of polymer chain which results in reduced diffusion of water into the polymer network.

Charge: The bioadhesive property of ionic polymer is always higher than that of non-ionic polymer. In neutral or slightly alkaline medium, the cationic polymer shows superior mucoadhesive property. It has been proven that, cationic high molecular weight polymer such as chitosan possess good bioadhesive property. [23]

Environment related factors

pH of polymer-substrate interface: The pH of polymer-mucin interface should be same as it is possible, because, the difference in

pH amongst the two systems may results in the transfer of charge due to the higher pH gradient. This may affect the mucoadhesion.

Applied strength: While placing a buccal mucoadhesive drug delivery system, sufficient strength should be applied in order to provide a good bioadhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient long time make the polymer become bioadhesive with mucus. [24]

Initial contact time: Greater the initial contact time between the mucoadhesive polymer and the mucus layer results in the increased swelling as well as interpenetration of the mucoadhesive polymer chain. Hence, increases the mucoadhesion strength of the polymer chain.

Moistening: Moistening is required for allowing the mucoadhesive polymer to spread over the surface. It creates a network of polymer chains of sufficient pore size. Through these pores, the interpenetration of polymer and mucin molecules takes place that results in increasing the mobility of polymer chains for the proper diffusion of mucoadhesive polymer in mucin layer. [25]

Physiological factors

Mucin turnover: High mucin turnover is not beneficial for the mucoadhesive property because of following reasons: The high mucin turn over limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though it has a good bioadhesive property.

Disease state: In some disease states, the secretion of mucus from the mucus membrane gets decreased (e.g., in Dry Mouth Syndrome and in old age). So that there is not sufficient amount of mucus present at the site of attachment of mucoadhesive dosage form.

Rate of renewal of mucosal cells: Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

Concomitant diseases: Concomitant diseases can alter the physicochemical properties of mucous or its quantity increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation.

Tissue movement: Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms. [26]

Overview of oral mucosa

The oral mucosa acts as the one of most important route for the delivery of drugs. It provides the delivery of drugs by both systemic as well as local pathways. The oral cavity contains a large surface area of mucus membranes for the complete absorption of various drugs. The total surface area of oral cavity i.e., lined by

mucus membranes is near about 100 cm². Following are the several parts of the oral cavity:

- The floor of mouth (sublingual)
- The buccal mucosa (cheeks)
- The gums (gingiva)
- The palatal mucosa and

- The lining of lips.

The oral mucosa mainly composed of three layers as shown in Figure 3.

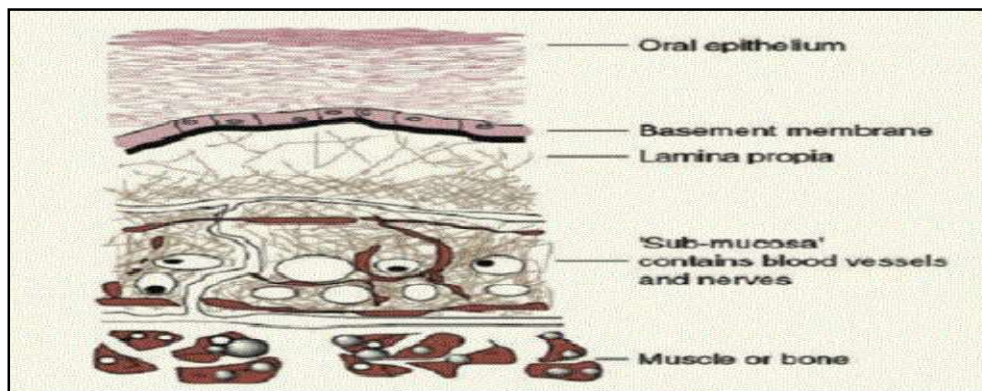


Figure 3: Anatomical structure of buccal route. [27]

Mucus composition

The oral mucus is generally secreted by various glands of oral cavity that are sublingual gland, parotid gland, and other salivary glands. The mucus is a translucent gel secreted by goblet cell or by special exocrine glands with the mucus cells. The components are given in Table 1. [28]

Table 1: Composition of mucus

Components	Percentage
Water	95%
Glycoproteins and lipids	0.5-5%
Mineral salts	1%
Free proteins	0.5-1%

Mucus glycoproteins are the high molecular proteins that contain attached oligo-polysaccharide units. The mucus contains following oligosaccharide units. L-fructose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine & Sialic acid

Functions of mucus

Cell-cell adhesion, Lubrication, Bioadhesion, Protective and Barrier

Buccal Mucoadhesive Films

These are single or multilayered thin film, round or oval consistently basically of bioadhesive polymeric layer and impermeable basically layer to provide a unidirectional flow of drug across buccal mucosa. Patches or film are preferred over

tablet because of their comfort and flexibility. They are formulated such that it can provide contact between bioadhesive formulation and mucosa. Thickness of patch is a constraint which cannot provide control release of drug for longer period of time. [29]

Basic Components of Buccal Drug Delivery System

Drug substance: The suitable active pharmaceutical ingredient or drug substance should be selected on the basis of its pharmacokinetic properties. The drug should be of following characteristics:

- The one time dose of drug should be small (dose ≤ 25 mg).
- The drug should be having short biological half life ranging from 2 to 8 hrs.
- The drugs showing first pass metabolism can be used for buccal drug delivery for avoiding the first pass metabolism. [30]

Bioadhesive polymer: The use of bio adhesive polymer determines the various parameters such as mucoadhesive strength, thickness, in-vitro release and the residence time of the drug delivery device. Generally the polymers with high molecular weight are preferred because; they show effective release rate controlling properties. [31]

- It should be inert.
- It should be compatible with the environment and drug.
- It should be adhere quickly with the mucus membrane and adherence should be long lasting for required time. [32]

The classification of Bioadhesive Polymers is given in Table 2.

Table 2: Classification of Bioadhesive Polymers

Criteria	Categories	Examples
Source	Semi natural	Agarose, chitosan, elatine, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Cellulose derivatives	Thiloated CMC, HEC, HPC, Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), PVA
Aqueous Solubility	Water-soluble	CP, HEC, HPC (water below 38.8°C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum

Backing membrane: Backing membrane used for the formulations should be impermeable to drug as well as mucus in order to prevent the unnecessary drug loss from all sides of the device. The materials used for preparing backing membrane should be inert, insoluble or should have low water solubility.^[33]

Plasticizer: The plasticizers are used in order to improve the folding endurance of the delivery device. They provide enough flexibility to the dosage form for improving its patient acceptability and patient compliance. Few examples of commonly used plasticizers are PEG-400, PEG-600, dibutyl phthalate, propylene glycol etc.

Permeation enhancers: These are the chemicals or liquids used to improve the permeation of drug from device into the mucus membrane. The permeation enhancers work by following mechanisms.

Mechanisms of action of permeation

- By reducing the viscosity of mucus.
- By increasing the fluidity of lipid bilayer membrane.
- By countering the enzymatic barrier.
- By increasing the thermodynamic activity of drugs.^[34]

Methods of preparation for buccal adhesive films

Solvent casting & Hot-melt extrusion

Solvent Casting: Buccal films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried. Steps in film casting. Water soluble hydrocolloids used to prepare films are HPMC, HPC, CMC, Pullulan and Pectin.^{[35][36]}

Hot-melt extrusion: In hot-melt extrusion, a blend of pharmaceutical ingredients is molten and then forced through an orifice (the die) to yield a more homogeneous material in different shapes, such as granules tablets, or films.

Hot metal extrusion is commonly used to prepare granules, sustained release tablets, transdermal and transmucosal drug delivery systems.^[37] However, only a handful of articles have reported the use of hot-melt extrusion for manufacturing mucoadhesive buccal films. Extensive researched on the use of hot-melt extrusion for the manufacture of mucoadhesive buccal films, evaluating different matrix formers and additives for the processing of the blend.^[38]

Mouth ulcer

Ulceration is a breach in the oral epithelium, which typically exposes nerve endings in the underlying lamina propria, resulting in pain or soreness, especially when eating spicy foods or citrus fruits. Patients vary enormously in the degree to which they suffer and complain of soreness in relation to oral ulceration. It is always important to exclude serious disorders such as oral cancer or other serious disease, but not all patients who complain of soreness have discernible organic disease. Conversely, some with serious disease have no pain.

Description and clinical forms of Mouth ulcers

Minor ulcer is the common variety, affecting about 80% of RAU (Recurrent Aphthous Ulcers) patients. It is characterized by painful round or oval shallow ulcers, regular in outline, less than 10 mm in diameter, with a grey-white pseudomembrane surrounded by a thin erythematous hallow. The lesions recur at varying frequencies (from every few years to almost constantly) and heal within 10–14 days without scarring.^[39] Major ulcer, also known as periaadenitis mucosa necrotica recurrens, occurs in approximately 10% of mouth ulcer patients. The lesions are similar in appearance to those of minor aphthae, but they are larger than 10 mm in diameter, single or multiple and very painful.^[40] The third and least common variety of mouth ulcers is herpetiform ulcer. The name is derived from the supposed resemblance to the intraoral lesions of primary herpes simplex (HSV) infection, but HSV cannot be isolated from Herpetiform lesions or from any other forms of mouth ulcers. Furthermore, Herpetiform lesions are not preceded by vesicular lesions, but develop - like all mouth lesions - directly as ulcers. The condition occurs more often in women and is associated with a later age of onset than other types of mouth ulcers.^[41] The three clinical types of mouth ulcer are shown in Figure 4.

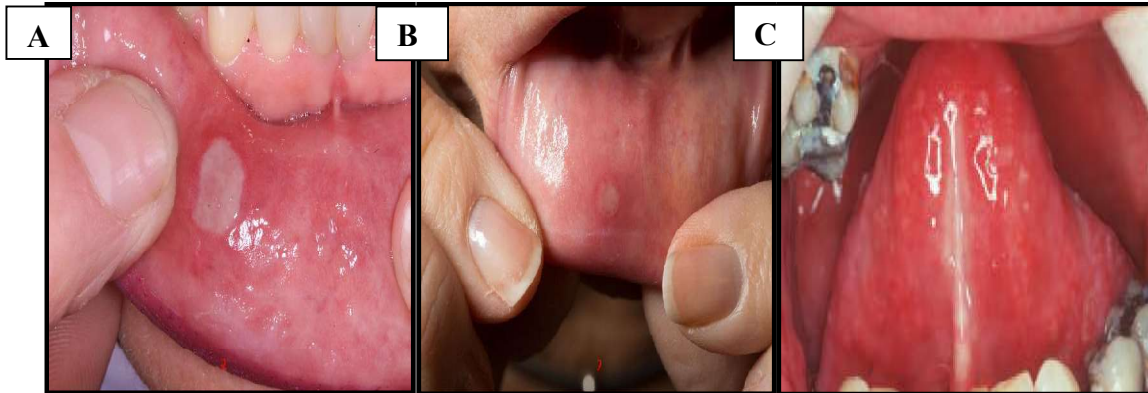


Figure 4: Images of three clinical types of mouth ulcers: Major Ulcer (A), minor ulcer (B) and herpetiform ulcer (C).¹⁴²¹

Aetiopathogenesis: Immune mechanisms appear at play in a person with a genetic predisposition to oral ulceration. A genetic predisposition is present, and there is a positive family history in about one third of patients with mouth ulcer. Immunological factors are also involved, with T helper cells predominating in the mouth ulcer lesions early on, along with some natural killer (NK) cells. Cytotoxic cells then appear in the lesions and there is evidence for an antibody dependent cellular cytotoxicity (ADCC) reaction.¹⁴³

Predisposing factors: Most people who suffer mouth ulcer are otherwise apparently completely well. In a few, predisposing factors may be identifiable, or suspected. These include:

- Stress
- Trauma
- Haematinic deficiency
- Sodium lauryl sulphate (SLS), a detergent in some oral healthcare products may produce oral ulceration.¹⁴³¹
- Cessation of smoking
- Gastrointestinal disorders particularly celiac disease (gluten-sensitive enteropathy) and Crohn’s disease in about 3% of patients.
- Endocrine factors in some women, those mouth ulcers are clearly related to the fall in progesterone level in the luteal phase of their menstrual cycle.
- Immune deficiency: ulcers similar to mouth ulcers may be seen in HIV and other immune defects.
- Food allergies: underlie mouth ulcers rarely.¹⁴⁴¹

Diagnosis: There is not any specific test unavailable for the diagnosis of mouth ulcers, so that the diagnosis is mainly based on the patient history as well as clinical features of the ulcer. Biopsy is rarely indicated, and is the last option for diagnosis after the failure of all other techniques.¹⁴⁵¹

Management and treatment of mouth ulcer

Mainly, Glucocorticoids and antimicrobial drug therapy are used as traditional treatments for mouth ulcers. These medications can be administered either topically (pastes, mouthrinses, intralesional injections etc.) or systemically by oral route.¹⁴⁶¹

Topical agents: Topical agents are used as first line choice of drugs for the treatment for mouth ulcers because of their advantages i.e. they are cheap, effective and safe. But the main problem with topical agents is their retention time on the surface of ulcer is less due to regular mucus secretions, which is the main barrier in obtaining effective drug delivery of topical agents.¹⁴⁷¹

Systemic medications: In case of severe and constantly recurring ulcers, sometimes, the topical treatment may not be enough. In such cases, the systemic medications are administered either orally or parentally.¹⁴⁸¹

The list of medicines used for management and treatment of mouth ulcers is shown in Table 3.

Table 3: The list of medicines used for management and treatment of mouth ulcers

Topical	Systemic		
	Specific	Non- specific	
Orabase TM	Vitamin B12	Corticosteroids	Montelukast
Sucralfate		Dapsone	TNF- α inhibitors
Escharotics		Colchicine	Levamisol
Laser treatment		Tetracycline	Cyclosporine A

OBJECTIVES OF THE REVIEW

The major objectives of this review work is

- To provide detailed information for controlled drug delivery of buccal adhesive film depending upon their

biopharmaceutical and dissolution characteristics (i.e., slow dissolving Vs non-dissolving).

- To detailing of delivery of the drug uni-directionally (i.e. directly into the buccal tissue), in order to avoid the unwanted drainage of drug from formulation.
- To provide better patient compliance as compared to other routes such as parenteral and oral route (as there is no invasion and swallowing required).
- To provide details regarding the buccal adhesive films with varying proportions of mucoadhesive polymer.

LITERATURE REVIEW

Esomeprazole mucoadhesive buccal tablets were formulated using mucoadhesive polymers like hydroxy propyl methyl cellulose K100M, Carbopol 934, HPMC K15M. Drug: polymer ratio for F5 was 1:1, this F5 (guar gum and carbopol -971P) formulation was considered as an optimized formulation among all these formulations because it released maximum amount of drug in desired period of 6 hrs and showed good swelling index properties.^[49]

Zidovudine mucoadhesive buccal patches were formulated using polymers i.e., HPMC E15, Sodium Alginate and gelatine. They concluded that the release of Zidovudine from the formulated patches followed zero order kinetics so that the drug release mechanism was controlled release.^[50]

The comparative study between benzydamine hydrochloride gel, lidocaine 5% gel and lidocaine 10% spray on endotracheal tube cuff as regards post operative sore throat was done. They concluded that the Benzydamine hydrochloride gel on the endotracheal tube cuff was a simple and effective method to reduce the incidence and severity of postoperative sore throat in relation to lidocaine and saline.^[51]

Bilayer patch of benzydamine HCl were formulated using solvent casting method. They used polymers such as HPMC E15 LV for the preparation of first layer in different concentrations and the second layer (Backing layer) was developed by using different polymers like eudragit RSPO, eudragit RSPO + EC, and eudragit NE30 D for efficient layer bonding. It also did not show layer separation of double layer patch. They concluded that all the patches were found to be stable over the storage period and conditions tested and did not shown any layer separation.^[52]

Solid dosage form for buccal drug delivery were formulated of Diltiazem Hydrochloride using various polymers i.e., Carbopol 971P (CP) and secondary polymers such as Hydroxy propyl methyl cellulose (HPMCK4M) and Psyllium husk in Six formulations. They concluded that the formulation B3 containing Carbopol 971P and HPMC K4M in the ratio of 1:5 showed good mucoadhesive strength (51.34 gm) and maximum drug release of 94.72% in 8 hrs. Swelling of tablets increased with increase in concentration of HPMC K4M.^[53]

Mucoadhesive film of HPMC for water insoluble drug was formulated using different plasticizers i.e. glycerine, Propylene glycol, Dibutyl phthalate, Triethanolamine and concluded that

buccal films prepared by using Propylene glycol as the plasticizer in the solvent methanol, promotes sustained drug release over a period of 6 hours of study and hence proves to be a good plasticizer in formulating buccal films which showed satisfactory results.^[54]

Mucoadhesive buccal film of Methyldopa were formulated using Hydroxy propyl methyl cellulose K-47 (HPMC K-47), poly vinyl pyrrolidone K-30 (PVP K-30), sodium CMC and ethyl cellulose. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation F5 (HPMC K-47 and PVP K-30). The correlation coefficient value (r) indicates the kinetic of drug release was zero order.^[55]

Buccal films of Ketorolac Tromethamine were formulated. These films were prepared by polymers like HPMC K 100M, HPMC E15, HPMC E50, Eudragit RLPO and developed by solvent casting method. Formulation F5 (HPMC E15-Polysorbate - Eudragit RLPO) exhibited best mucoadhesive performance and matrix controlled release. Swelling behaviour and duration of mucoadhesion are critical factors in the selection of satisfactory formulation.^[56]

Mucoadhesive buccal film of Lisinopril were formulated using various polymers like HPMC K4M, sodium CMC, PVP K30, eudragit RL 100, carbopol 934 by solvent casting method. They concluded that, based on *in vitro* drug release, formulation F12 with 4% HPMC K4M, 0.5% PVP K30, 1% Sodium CMC and 5% Tween80 exhibited a extended drug release of 98.41% in 8 hours. The optimized formulation followed zero order kinetics.^[57]

Ropinirole buccal patches, prepared by using different mucoadhesive polymers by solvent casting technique. They concluded that, the release of Ropinirole from all patches followed zero order and mechanism was diffusion rate limited. Incorporation of hydrophilic polymer PVP K-30 enhanced the drug release, swelling index but significantly decreased the mucoadhesive strength. Addition of carbopol 934p decreased the drug release, swelling index but increased the mucoadhesive time and mucoadhesive strength.^[58]

A study was conducted on Formulation and in vitro evaluation of Losartan Potassium mucoadhesive buccal tablets. They used mucoadhesive polymers such as Carbopol -940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in alone and in combination as release retarding agent to prolong the drug release and to avoid first pass metabolism. Ex-vivo mucoadhesive strength, ex vivo residence time and in-vitro release studies showed that formulation F10 (sodium alginate and HPMC K100M) containing 1:1.25 ratio of drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release (91.33 % after 12 hrs).^[59]

The buccal patches of Simvastatin were formulated. The buccal patches were prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC. The formulation containing eudragit-RS100 and PVP (1:1) showed the maximum and faster release.^[60]

Mucoadhesive buccal patches of Tramadol hydrochloride were formulated using various concentrations of Chitosan polymer by solvent casting technique. The patches were exhibited controlled release more than six hours. The *in vitro* release data were fit to different equation and kinetic models to explain release profiles. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation R6. The formulation was found be right and suitable candidate for the formulation of Tramadol HCL mucoadhesive buccal patches for therapeutic use.¹⁶¹

The bilayerd films were prepared by solvent casting technique using different concentration of two polymers namely, sodium alginate and pectin. The backing membrane was prepared by using sodium alginate. The drug containing layer was prepared by using pectin. He concluded that the developed mucoadhesive buccal patches of diclofenac sodium can sustain the drug release, improve the bioavailability of the drug and overcome the first pass metabolism of the drug.¹⁶²

Mucoadhesive buccal patches of Pantoprazole were formulated and evaluated using polymers like HPMC and PVP in various proportions which offers an attractive route of administration for systemic drug delivery. From the evaluation results it was concluded that such buccal patches of Pantoprazole provided buccal delivery for prolonged periods in the management of gastro esophageal reflux disease, which can be a good way to bypass the extensive hepatic first-pass metabolism.¹⁶³

Buccal tablets of Metoprolol Tartrate were formulated using different mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination. The prepared tablets were evaluated for bioadhesive strength and in-vitro drug release. In-vitro bioadhesive strength and in-vitro release studies showed that formulation containing 1:1.25 ratio of drug and polymer (Carbopol-934 and HPMC K4M) combination showed optimum bioadhesive and exhibited optimum drug release (77.33 ± 0.23).¹⁶⁴

Propranolol hydrochloride buccal mucoadhesive gel was formulated using Natural Mucoadhesive agent obtained from the Fruits of Ficus carica L. The formulation F1, F3, F4 and F5 showed Fickian diffusion, formulation F2 showed Anomalous (non-Fickian) diffusion.¹⁶⁵

Monolayered buccal patch containing Tizanidine HCl were formulated using the emulsi- fication solvent evaporation method. Fourteen formulations were prepared using the polymers Eudragit RS 100 or Eudragit RL 100 and chitosan. Formulations prepared using Eudragit polymer alone exhibited satisfactory physicochemical properties but lacked a gradual in vitro drug release pattern. Incorporation of chitosan into formulations resulted in the formation of a porous structure which did exhibit gradual release of drug.¹⁶⁶

The mucoadhesive buccal patches of Methotrexate were developed. It used the backing membrane prepared by ethyl cellulose (5%) in mixture of acetone and isopropyl alcohol (60:40). Glycerol (5%) was added as plasticizer. The mucoadhesive polymers used were Sodium Alginate, carbopol-934, sodium carboxy methyl cellulose and polyvinyl pyrrolidone. The

cumulative drug release of the formulation containing sodium alginate with a secondary polymer was found in order of Sodium alginate > carbopol-934 > Sodium Carboxy methyl cellulose > polyvinyl pyrrolidone at the end of 8 hours.¹⁶⁷

Buccal tablets of Piroxicam were formulated using HPMC K4M and Carbopol-934 in different ratios. In this study H3 formulation comprising of piroxicam and HPMC K4M (1:3) show edoptimum drug release and satisfactory bioadhesive properties.¹⁶⁸ Mucoadhesive patches of Terbutaline sulphate were formulated. The patches were prepared by the solvent casting method using Hydroxyl propyl methyl cellulose (HPMC cps50) as basic polymer and Carbopol 934, Eudragit RL 100, and Ethyl cellulose were taken in various ratios and 6 different formulations were made. They concluded that the BP3 formulation containing Terbutaline sulphate, HPMC: Eudragit RL100 (4:1) Glycerine, Acetone and Tween 80 showed a release of 96.36% after 12 hours in phosphate buffer (pH, 6.8).¹⁶⁹

The buccal mucoadhesive patches of Prochlorperazine were formulated using various concentrations of HPMC E15 and Polyester backing membrane. They concluded that the formulation containing 2500 mg of HPMC E15 and 375 μ l of Propylene glycol was the optimized formulation after evaluating it in-vitro as well as ex-vivo studies.¹⁷⁰ Buccal mucoadhesive drug delivery systems of Metoprolol Tartrate were formulated using the mucoadhesive polymers i.e., Carbopol-934, hydroxy methyl propyl cellulose, hydroxyl ethyl cellulose and sodium carboxy methyl cellulose. The best mucoadhesive performance and in-vitro drug release profile were exhibited by tablets containing hydroxyethyl cellulose and Carbopol-934 in 1:2.¹⁷¹

CONCLUSION

The main objective of the present review work was to enlighten on the theories to deliver the drug in a controlled manner in order to improve the therapeutic efficacy by increasing the mucoadhesive residence time of the dosage form at the site of application. The buccal adhesive films can be evaluated based upon their physicochemical characteristics like thickness, weight variation, folding endurance, surface pH, percent moisture absorption, percent moisture loss, swelling percentage, percent drug content, *in vitro* drug released, *ex vivo* mucoadhesive strength and *ex vivo* mucoadhesive residence time. The % *in vitro* drug release data of all optimized formulations can be subjected to various *in vitro* release kinetic models such as zero order, first order, Higuchi model and Korsmeyer Peppas's model to find out the exact mechanism of drug release from the prepared formulations. The final formulation can be further subjected for one month accelerated stability studies. The results of accelerated stability studies confirmed the better stability of the final formulation. It is concluded that the buccal adhesive films can achieved the set objectives to deliver the drug in a controlled manner in order to improve the therapeutic efficacy by increasing the mucoadhesive residence time of the dosage form at the site of application.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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