Buccoadhesive Dosage Form Containing Antifungal Agent for Treating Oropharyngeal Candidiasis: A Review

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Abstract: Oral candidiasis is a common fungal infection in patients with an impaired immune system, such as those undergoing chemotherapy for cancer and patients with AIDS (Acquired immune deficiency syndrome). The majority of infections are due to Candida albicans although other species such as Candida glabrata, Candida tropicalis, Candida krusei and Candida parapsilosis are increasingly isolated. The objective of this article is to review candidiasis, types of candidiasis, discussing the structure and environment and permeability of the oral mucosa. Buccoadhesive drug delivery will also be reviewed with an emphasis on Bioadhesion, theories of Bioadhesion, investigated mucoadhesive polymer's and Buccoadhesive tablet/film containing antifungal agent for treating oropharyngeal candidiasis.

Keywords: AIDS, buccoadhesive, cancer, candida species, mucosa, oral candidiasis.

INTRODUCTION

Oral candidiasis is an opportunistic infection of the oral cavity. It is common and under diagnosed among the elderly, particularly in those who wear dentures and in many cases is avoidable with a good mouth care regimen. It can also be a mark of systemic disease, such as diabetes mellitus and is a common problem among the immunocompromised. Oral candidiasis is caused by an overgrowth or infection of the oral cavity by a yeast-like fungus, Candida [1, 2]. There are several types of candidiasis, ranging from superficial infections of the skin, nails and mucous membranes, to candidemia and deep-seated systemic infections. Oropharyngeal candidiasis is a common manifestation in immunocompromised patients, in elderly individuals undergoing immunosuppressive therapy for cancer or organ transplantation and those exposed to broad spectrum antibiotics. Most notably, oropharyngeal candidiasis is a major problem in individuals infected with HIV (Human immunodeficiency virus). These individuals may suffer from painful, recurrent oral candidiasis which may be complicated by esophageal candidiasis. The latter may rarely lead to gastrointestinal bleeding, perforation or disseminated candidiasis. Other, more difficult to recognize, clinical manifestations of oral candida infection include atrophic candidiasis and angular cheilitis [3].

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract, that prohibit oral administration of certain classes of drugs. Consequently, other absorptive mucosae are considered as potential sites for drug administration.

Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre systemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption [4-8].

Even though the rectal, vaginal, and ocular mucosae all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. The oral cavity, on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage [9, 10], and the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens [11]. Furthermore, oral transmucosal drug delivery by passes first pass effect and avoids pre systemic elimination in the gastrointestinal tract.

Mucoadhesive buccal drug delivery is advantageous in treating not only systemic infections but also local infections of oral mucosa. Buccoadhesive tablets that are applied directly to the affected mucosal regions have the potential to supply the site of action with effective drug levels and sustain these levels over a long period of time [12].

CANDIDIASIS

Candidiasis is a fungal infection of mouth and throat. It is caused by candida species. Candida are small (4–6 μm), oval, thin-walled yeast like fungi that reproduce by budding or fission. The genus Candida is comprised of over 200 species. The medically significant Candida species include: Candida albicans, Candida (Torulopsis) glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei, Candida kefyr, Candida guilliermondii, Candida lusitaniae, Candida stellatoidea, and Candida dubliniensis [13].

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*Candida albicans* remains the major fungal pathogen of man and the most common cause of mucosal and systemic fungal infection. *Candida glabrata* has become important because of its increasing incidence worldwide and decreased susceptibility to antifungals. Its emergence is largely due to an increased immunocompromised patient population and widespread use of antifungal drugs [14, 15].

**TYPES OF CANDIDIASIS**

**Oropharyngeal Candidiasis**

Oropharyngeal candidiasis (OPC) is most prevalent in infants, the elderly, and compromised hosts and occurs in association with serious underlying conditions including diabetes, leukemia, neoplasia, steroid use, antimicrobial therapy, radiation therapy, and HIV infection [16, 17]. One group of investigators reported that 28% of cancer patients not receiving antifungal prophylaxis developed OPC and another group observed OPC in 57% of immunocompromised patients [18]. Patients at greatest risk of developing OPC include those receiving corticosteroids and with prolonged neutropenia who are colonized with a *Candida* species [19]. Approximately 80%–90% of patients with HIV-infection will develop OPC at some stage of their disease. Symptoms of oral thrush are variable, including a sore, painful mouth, burning tongue and dysphagia [20, 21]. 60% of untreated patients develop an AIDS-related infection or Kaposi’s sarcoma within two years of the appearance of OPC [22].

The ability of *Candida albicans* to adhere to buccal epithelial cells is critical in establishing oral colonization; *Candida albicans* adheres better to epithelial cells than non-albicans *Candida* species. Low numbers of organisms are the result of effective antifungal host defense mechanisms in the oral cavity. Low salivary flow rates correlate with higher prevalence rate of *Candida*. Genotyping of *Candida* strains obtained from HIV-positive patients with OPC and esophageal candidiasis compared to isolates from healthy individuals indicate an identical distribution frequency, suggesting that HIV associated candidiasis is not caused by unique or particularly virulent strains, but from defects in host defenses [23].

**ACUTE PSEUDOMEMBRANOUS CANDIDIASIS (EXUDATIVE)**

This most common form of OPC, especially in HIV-positive persons, presents with a whitish-yellow thick curd-like exudate on mucosal surfaces. Plaques may be small and discrete or confluent lesions involving the entire oral mucosa, and consist of necrotic material and desquamated epithelial cells, penetrated by hyphae and yeast cells which continue their invasion into the stratum corneum [24].

**ESOPHAGEAL CANDIDIASIS**

The prevalence of *Candida* esophagitis has increased because of AIDS, as well as the increased pool of transplant recipients, cancer and other severely immunocompromised patients. *Candida* microorganisms are frequently recovered from the esophageal surface and reach the esophagus in oral secretions. Predisposing factors include exposure to local irradiation, recent cytotoxic chemotherapy, antibiotics, corticosteroids, and neutropenia. The high prevalence of esophageal candidiasis in patients with AIDS indicates the critical role of cell mediated immunity in normally protecting the esophagus from *Candida* invasion. Esophageal candidiasis in an HIV-positive patient may be the first manifestation of AIDS, typically occurring at lower CD4 counts less than 100 cells/mm³ [25].

*Candida* esophagitis presents with dysphagia, odynophagia, and retrosternal pain. *Candida* esophagitis in patients with AIDS may be entirely asymptomatic in spite of extensive esophageal involvement [26]. Esophageal candidiasis is classified on the basis of endoscopic appearance: Type I, a few white or beige plaques, up to 2 mm in diameter; Type II, plaques are more numerous, larger than 2 mm in diameter; Type III, confluent, linear and nodular elevated plaques with hyperemia and frank ulceration and Type IV, similar to Type III but with increased mucosal friability and occasional narrowing of the lumen [27]. Uncommon complications of esophagitis include perforation, aortic-esophageal fistula and rarely, extensive necrosis destroying the entire esophageal mucosa [28, 29].

**GENERALIZED CUTANEOUS CANDIDIASIS**

Generalized Cutaneous Candidiasis is a rare form of candidiasis that manifests as a diffuse eruption over the trunk, thorax, and extremities. Patients have a history of generalized pruritus, with increased severity in the genitocrural folds, anal region, axillae, hands, and feet. Examination reveals a widespread rash that begins as individual vesicles that evolve into large confluent areas [30].

**VULVOVAGINAL CANDIDIASIS**

In United States, *Candida* vaginitis is the second most common vaginal infection. During the childbearing years, 75% of women experience at least one episode of vulvovaginal candidiasis (VVC), and 40%–50% of these women experience a second attack [31]. Several factors are associated with increased rates of a symptomatic vaginal colonization with *Candida* as well as *Candida* vaginitis including pregnancy (30%–40%), oral contraceptives with a high estrogen content, and uncontrolled diabetes mellitus. Other predisposing factors include corticosteroids, antimicrobial therapy, intrauterine devices, and high frequency of coitus. Factors that enhance or facilitate germination (e.g., estrogen therapy, pregnancy) tend to precipitate symptomatic vaginitis whereas measures that inhibit germination (e.g., bacterial flora) may prevent acute vaginitis in women who are asymptomatic carriers of *Candida* [32].

**CANDIDEMIA AND DISSEMINATED CANDIDIASIS**

Candidemia or systemic candidiasis has been divided into four groups or syndromes, namely, catheter-related candidiasis, acute disseminated candidiasis, chronic disseminated candidiasis (hepatosplenic candidiasis), and deep organ candidiasis. Although hematogenous involvement occurs at some stage in the evolution of each, only the first two syn-
dromes are associated strongly with documented candidemia. Hence use of the term candidemia only as a marker of invasive candidiasis results in the underestimation of the true incidence of invasive candidiasis [33]. The last 4 decades have witnessed a dramatic increase in the incidence of candidemia, originating in tertiary care centers and now observed in virtually all type hospitals [34, 35].

The source of candidemia remains poorly understood in spite of the aforementioned risk factors. In neutropenic individuals, gut colonization is likely responsible for most cases of candidemia. In some tertiary care centers, *Candida albicans* is no longer the most frequent bloodstream isolate, being replaced by *Candida glabrata*, which surpassed *Candida tropicalis* as the most prevalent non-*albicans* species and currently cause 3%-35% of all candidemias [36-38]. Clinical aspects of candidemia are extremely variable. Patients present with fever alone without organ-specific manifestations, or a wide spectrum of symptoms and signs, including fulminant sepsis. Accordingly, acute candidemia indistinguishable from bacterial sepsis and septic shock. In general, there are no specific clinical features of candidemia associated with individual *Candida* species [39].

**OVERVIEW OF ORAL MUCOSA**

**Structure**

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium of the buccal mucosa is about 40-50 cell layers thick. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers [40]. The turnover time for the buccal epithelium has been estimated at 5-6 days. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of the gingivae and hard palate are keratinized similar to the epidermis and mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelium contains neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia [41, 42-44]. Fig. (1) shows various layers of oral mucosa.

**PERMEABILITY**

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin [45]. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal and buccal greater than palatal [41]. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called ‘membrane coating granules’ (MCG) [40]. When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200μm of the superficial layer. According to permeation studies carried out using number of very large molecular weight tracers, it seems apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells [46, 47].

**SECRETION OF SALIVA**

The mucous membrane lining in the mouth contains many minute glands called buccal glands, which pour their secretions into the mouth, the chief secretion is supplied by three pairs of glands, namely, the parotid (under and in front of the ear), the sub maxillary (below the jaw), and the sublingual (under the tongue) glands. Blood is richly supplied to the salivary glands and their ducts by branches of the external carotid artery and afterwards, traveling through the many branch arteries and capillaries, returns to the systemic circulation via the jugular veins [41]. In addition to the protective function afforded by the oral mucosa, it also has the ability to maintain a moist surface, which enhances permeability of the membrane to drugs [48].

The presence of saliva in the mouth is important to drug absorption for two main reasons:

1. Drug permeation across moist (mucous) membranes occurs much more readily than across non mucous membranes.

2. Drugs are commonly administered to the mouth in the clinical setting in a solid form. The drug must, therefore, first dissolve in saliva before it can be absorbed across the oral mucosa; that is, the drug cannot be absorbed directly from a tablet.

**MECHANISMS INVOLVED IN DRUG ABSORPTION ACROSS THE ORAL MUCOSA**

The mechanisms by which drugs cross biologic lipid membranes are passive diffusion, facilitated diffusion, active transport, and pinocytosis. Small, water-soluble molecules may pass through small, water-filled pores. The main mechanism involved in drug transfer across the oral mucosa, common with all regions of the gastrointestinal tract, is passive diffusion, although facilitated diffusion has also been shown to take place, primarily with nutrients.
MUCOADHESION OR BIOADHESION

The term "Bioadhesion" is the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface [49].

THEORIES OF BIOADHESION

Five theories have been suggested to play a major role in bioadhesion, namely, adsorption, diffusion, electronic, fracture, and wetting theories [50, 51]. In the ‘adsorption theory’, primary and secondary chemical bonds of the covalent and non-covalent (electrostatic and Vander Waals forces, hydrogen, and hydrophobic bonds) types are formed upon initial contact between the mucus and the mucoadhesive polymer. Most of the initial interfacial bonding forces are attributed to non-covalent forces. The formation of secondary chemical bonds greatly depends on properties of the polymer, which will be covered briefly in the next section. The basis of the ‘diffusion theory’ is chain entanglement between glycoprotein’s of the mucus and the mucoadhesive polymer. Upon initial contact between these two polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and the diffusion coefficient of the bioadhesive polymer are among the factors which influence the inter-diffusion of the macromolecule network. The third theory is the ‘electronic theory’. Because of different electronic properties of the mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occurs. Electron transfer contributes to formation of a charged double layer at the interface of the mucus and the polymer, which results in forces of attraction in this region and inter-diffusion of the two surfaces. The ‘fracture theory’ relates the force required for the detachment of polymers from the mucus to the strength of their adhesive bond. It has been found that the work fracture is greater when the network strands are longer or the degree of cross-linking is reduced [52]. Finally, the ‘wetting theory’ describes the ability...
of a bioadhesive polymer to spread on biological surfaces. This theory is predominantly applicable to liquid bioadhesive systems. Moderately wettable polymers have been shown to exhibit optimal adhesion to human endothelial cells [53].

FACTORS AFFECTING BIOADHESION

a. Flexibility

The increased chain interpenetration was attributed to the increased structural flexibility of the polymer upon incorporation of poly (ethylene glycol). In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network.

b. Hydration

Hydration is required for a mucoadhesive polymer to expand and create a proper ‘macromolecular mesh’ of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin.

c. Cross-Linking Density

Increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin [50].

d. Concentration

For each polymer, there is a critical concentration, above which the polymer produces an ‘unperturbed’ state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, very high concentrations of polymers do not necessarily improve mucoadhesive properties [51].

e. Molecular Weight

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000 [54].

f. Hydrogen Bonding Capacity

Mucoadhesion to occur desired polymers must have functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential [55].

g. Charge

Strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium [56].

h. Environmental Factors

The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer. Saliva, as a dissolution medium, affects the behavior of the polymer. Depending on the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5 [57]. Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the oral cavity. Movements within the oral cavity continue even during sleep, and can potentially lead to the detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is necessary in order to avoid many of these interfering factors [58].

MUCOADHESIVE POLYMERS

Bioadhesive polymers have extensively been employed in buccal drug delivery systems. Bioadhesive polymers are defined as polymers that can adhere onto a biological substrate. Some of the necessary structural characteristics for bioadhesive polymers include strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility, and surface energy properties favoring spreading on a mucus layer [59]. Recent research carried on various mucoadhesive polymers and the objective of the research carried out is listed in Table 1.

BUCCOADHESIVE DOSAGE FORMS

Buccoadhesive drug delivery systems have been used to treat oral infections like oropharyngeal candidiasis due to its greater ability to adhere to the infected region for a longer period of time and release the drug at controlled rate for prolonged period of time. Buccoadhesive dosage forms can be categorized into three types based on their geometry. Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. In type II devices, an impermeable backing layer is superimposed on top of the drug-loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity. Type III is a unidirectional release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa. Buccal dosage forms can also be classified as either a “reservoir” or “matrix” type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug’s release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network. In general, dosage forms designed for buccal drug delivery should be small and flexible enough to be acceptable for patients, and should not cause irritation. Other desired characteristics of a Buccoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good bioadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. Buccoadhesive dosage forms include tablets, patches, films, and semisolids (gels and ointments). Buccal mucoadhesive dosage forms can also used for local
therapy. Van Roey and Haxaire have developed buccal mucoadhesive tablets containing low dose (10 mg) of an antifungal drug, Miconazole Nitrate. Hence buccal mucoadhesive drug delivery can be used for local delivery of antifungals to treat oropharyngeal candidiasis [80].

**BUCCAL TABLETS**

Buccal tablets are small, flat, and oval, with a diameter of approximately 5–8mm. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth.

Bioadhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used. Tablets intended for buccal administration by insertion into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure only to give a hard tablet. In order to achieve unidirectional release, every face of the tablet, except the one that is in contact with the buccal mucosa, can be coated with water impermeable materials, such as ethyl cellulose, hydrogenated castor oil, etc., using either compression or spray coating. Multilayered tablets may be prepared by sequentially adding and compressing the ingredients layer by layer. Iscan et al., [81] compared a number of parameters of a specially formulated buccal bioadhesive captopril tablet with that of a conventional tablet. The buccal formulation provided controlled release of captopril with a smooth plasma level profile and a

<table>
<thead>
<tr>
<th>Polymers Studied</th>
<th>Objective of the Research</th>
<th>References</th>
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<tr>
<td>HPC and CP</td>
<td>Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination.</td>
<td>[60]</td>
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<tr>
<td>HPC and CP</td>
<td>Measured Bioadhesive property using mouse peritoneal membrane.</td>
<td>[61]</td>
</tr>
<tr>
<td>CP, HPC, PVP, CMC</td>
<td>Studied inter polymer complexation and its effects on bioadhesive strength.</td>
<td>[62]</td>
</tr>
<tr>
<td>CP and HPMC</td>
<td>Formulation and evaluation of buccoadhesive controlled release delivery systems.</td>
<td>[63]</td>
</tr>
<tr>
<td>HPC, HEC, PVP, and PVA</td>
<td>Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer.</td>
<td>[64]</td>
</tr>
<tr>
<td>CP, PIP, and PIB</td>
<td>Used a two roll milling method to prepare a new bioadhesive patch formulation.</td>
<td>[65]</td>
</tr>
<tr>
<td>Chitosan, HPC, CMC, Pectin, Xantham gum, and Polycarboxphil</td>
<td>Evaluate mucoadhesive properties by routinely measuring the detachment force form pig intestinal mucosa.</td>
<td>[66]</td>
</tr>
<tr>
<td>Hyaluronic acid benzyl esters, Polycarboxphil, and HPMC</td>
<td>Evaluate mucoadhesive properties.</td>
<td>[67]</td>
</tr>
<tr>
<td>Polycarboxphil</td>
<td>Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs.</td>
<td>[68]</td>
</tr>
<tr>
<td>HPC, HPMC, CP and CMC.</td>
<td>Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion.</td>
<td>[69]</td>
</tr>
<tr>
<td>Poly (acrylic acid-comethyl methacrylate)</td>
<td>Effects of polymer structural features on mucoadhesion.</td>
<td>[70, 71]</td>
</tr>
<tr>
<td>Poly (acrylic acid-co- butyl acrylate)</td>
<td>Relationships between structure and adhesion for mucoadhesive polymers.</td>
<td>[72]</td>
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<td>HEMA copolymerized with polytetramethylene glycol</td>
<td>Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine.</td>
<td>[73]</td>
</tr>
<tr>
<td>Cydot® by 3M (bioadhesive polymeric blend of CP and PIB)</td>
<td>Patch system for buccal mucoadhesive drug delivery.</td>
<td>[74, 75]</td>
</tr>
<tr>
<td>CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride</td>
<td>Mucoadhesive gels for intra oral delivery.</td>
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<tr>
<td>CMC, CP, Polyethylene oxide, Polymethylvinylylether/ Maleic anhydride (PME/MA), Tragacanth</td>
<td>Buccal mucoadhesive device for controlled release anticandidal device - CMC tablets yielded the highest adhesive force.</td>
<td>[77]</td>
</tr>
<tr>
<td>HPMC and polycarboxphil(PC)</td>
<td>Buccal mucoadhesive tablets with optimum blend ratio highest force of 80:20 PC to HPMC yielding the adhesion.</td>
<td>[78]</td>
</tr>
<tr>
<td>Drum dried waxy maize starch (DDWM), Carbopol 974P, and Sodium stearyl fumarate.</td>
<td>Bioadhesive erodible buccal tablet for progesterone delivery.</td>
<td>[79]</td>
</tr>
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</table>
long duration of action; however, its bioavailability was 40% via the buccal route as compared to 65% following an oral dose.

**BUCCAL FILMS**

Films are the most recently developed dosage form for buccal administration.

Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Bioadhesive films are similar to laminated patches in terms of their flexibility and manufacturing process.

They are usually manufactured by a solvent casting method. The drug and polymer(s) are first dissolved in a casting solvent or solvent mixture. The solution is then cast into films, dried, and finally laminated with a backing layer or a release liner. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used. These drawbacks can be overcome by the hot-melt extrusion method recently reported by Repka et al. [92]. List of investigated buccal tablets and films containing antifungal for treating oral candidiasis is given in Fig. (2).

List of commercial available dosage form is given in Table 2.

**CONCLUSION**

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. Buccoadhesive drug delivery system utilize the property of bioadhesion of certain water soluble polymer which become adhesive on hydration and hence can be used for targeting a antifungal drug to oral mucosa for treating local infections like oropharyngeal candidiasis. By utilizing such a system high dose of systemic antifungals for treating oropharyngeal candidiasis can be avoided which may cause unwanted side effects.

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**Table 2**

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Polymers used</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Lactoferrin</td>
<td>Sodium alginate</td>
<td>[82]</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>HPMC, Sodium CMC and CP 934P</td>
<td>[83]</td>
</tr>
<tr>
<td>or Benzydamine</td>
<td>HPMC, Gelatin/HPMC and Gelatin/Sodium CMC</td>
<td>[84]</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>HEC, HPMC, or Na CMC combined with CP 940, CP 971 or PC</td>
<td>[85]</td>
</tr>
<tr>
<td>Miconazole Nitrate</td>
<td>Mixtures of HPMC, Sodium CMC, CP 934P and Sodium Alginate</td>
<td>[86]</td>
</tr>
<tr>
<td>Miconazole Nitrate</td>
<td>Thermally modified maize starch (dram-dried waxy maize)</td>
<td>[87-90]</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Carbomer, HPMC</td>
<td>[91]</td>
</tr>
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<td>Clotrimazole</td>
<td>Sodium CMC, Carbopol 974P</td>
<td>[93]</td>
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<tr>
<td>Fluconazole</td>
<td>HPMC, HEC, Chitosan, Eudragit and sodium alginate</td>
<td>[94]</td>
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<tr>
<td>Nystatin</td>
<td>Carbomer, CMC</td>
<td>[95]</td>
</tr>
<tr>
<td>Miconazole</td>
<td>SCMC, Chitosan, PVA, HEC, HPMC</td>
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</tr>
<tr>
<td>Chlorhexidine di gluconate</td>
<td>Chitosan</td>
<td>[97]</td>
</tr>
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</table>

**Fig. (2).** List of investigated buccal tablets and films for oral candidiasis.
Table 2. Commercial Available Antifungal Dosage Forms

<table>
<thead>
<tr>
<th>Gel</th>
<th>Miconazole</th>
<th>Canticid</th>
<th>Gyno-daktarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creams</td>
<td>Miconazole</td>
<td>Micogel</td>
<td>Vagibact</td>
</tr>
<tr>
<td>Ovule</td>
<td>Miconazole</td>
<td>Gyno-daktarin</td>
<td>Zole ovule</td>
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<tr>
<td>Tablet</td>
<td>Clotrimazole</td>
<td>Candid</td>
<td>Fungicide</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Fungizole</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Neral</td>
</tr>
<tr>
<td>Vg-tablet</td>
<td>Clotrimazole</td>
<td>Antican</td>
<td>Adcon</td>
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<td>Fluconazole</td>
<td>Anticanz</td>
<td>Cancap, VT</td>
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<td></td>
<td>Itraconazole</td>
<td>Candidral</td>
<td>Flucovar</td>
</tr>
</tbody>
</table>

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ABBREVIATIONS

AIDS = Acquired immune deficiency syndrome
CMC = Carboxymethyl cellulose
CP = Carbopol 934P
HEC = Hydroxy ethyl cellulose
HEMA = Hydroxyl ethyl methacrylate
HIV = Human immunodeficiency virus
HPC = Hydroxyl propyl cellulose
HPMC = Hydroxy propyl methyl cellulose
MA = Maleic anhydride
MCG = Membrane coating granule
OPC = Oropharyngeal candidiasis
PC = Poly Carbophil
PIB = Poly (isobutylene)
PPI = Poly (isoprene)
PMEA = Polymethylvinylether
PVA = Polyvinyl alcohol
PVP = Poly (vinyl pyrrolidone)
SCMC = Sodium carboxy methyl cellulose
VVC = Vulvovaginal candidiasis

REFERENCES


