Review article

Manufacture and characterization of mucoadhesive buccal films

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ABSTRACT

The buccal route of administration has a number of advantages including bypassing the gastrointestinal tract and the hepatic first pass effect. Mucoadhesive films are retentive dosage forms and release drug directly into a biological substrate. Furthermore, films have improved patient compliance due to their small size and reduced thickness, compared for example to lozenges and tablets. The development of mucoadhesive buccal films has increased dramatically over the past decade because it is a promising delivery alternative to various therapeutic classes including peptides, vaccines, and nanoparticles. The "film casting process" involves casting of aqueous solutions and/or organic solvents to yield films suitable for this administration route. Over the last decade, hot-melt extrusion has been explored as an alternative manufacturing process and has yielded promising results. Characterization of critical properties such as the mucoadhesive strength, drug content uniformity, and permeation rate represent the major research areas in the design of buccal films. This review will consider the literature that describes the manufacture and characterization of mucoadhesive buccal films.

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1. Introduction

Films as dosage forms have gained relevance in the pharmaceutical arena as novel, patient friendly, convenient products. More recently, orally disintegrating films (or strips) have come to light, thanks to their improved mechanical properties [1]. This translates into a less friable dosage form compared to most commercialized orally disintegrating tablets, which usually require special packaging [2]. Mucoadhesive buccal films share some of these advantages and more. Due to their small size and thickness, they have improved patient compliance, compared to tablets [3–5]. Moreover, since mucoadhesion implies attachment to the buccal mucosa, films can be formulated to exhibit a systemic or local action [6]. Many mucoadhesive buccal films have been formulated to release drug locally in order to treat fungal infections in the oral cavity such as oral candidiasis [7–11]. Due to the versatility of the manufacturing processes, the release can be oriented either towards the buccal mucosa or towards the oral cavity; in this latter case, it can provide controlled release via gastrointestinal (GI) tract administration. Alternatively, films can be formulated to release the drug towards the buccal mucosa. Films releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek [12]. Previously, many articles have reviewed the

development of mucoadhesive buccal systems in global terms [13–17], or their specific attributes such as permeation enhancers [18] or mucoadhesive polymers [19–21]. This article reviews the relevant literature which provides a background for understanding the rationale behind the formulation of mucoadhesive buccal films, as well as reviewing the most crucial characterization techniques for these dosage forms. The reader should notice that the literature use the term film and patch interchangeably.

1.1. Physicochemical properties of the oral mucosa

The oral mucosa presents differently depending on the region of the oral cavity being considered [22]. The masticatory mucosa covers those areas that are involved in mechanical processes, such as mastication or speech, and includes the gingival and hard palate. This masticatory region is stratified and has a keratinized layer on its surface, similar to the structure found at the epidermis, and covers about 25% of the oral cavity [23]. The specialized mucosa covers about 15%, corresponding to the dorsum of the tongue, and is a stratified tissue with keratinized as well as non-keratinized domains [24]. Finally, the lining mucosa covers the remaining 60% of the oral cavity, consisting of the inner cheeks, floor of the mouth, and underside of the tongue. This lining epithelium is stratified and non-keratinized on its surface [25]. The buccal mucosa covers the inner cheeks and is classified as part of the lining mucosa, having approximately 40–50 cell layers resulting in an epithelium 500–600 μm thick (Fig. 1) [26]. The epithelium is attached to underlying structures by a connective tissue or lamina propia, separated by a basal lamina. These lining mucosa and the lamina

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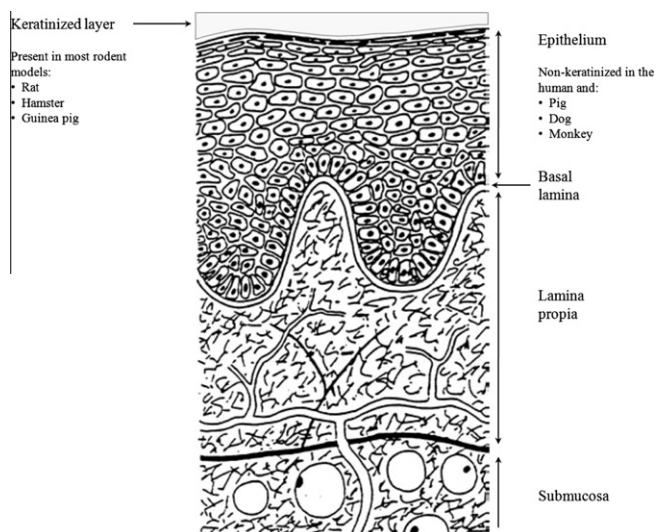E-mail address: jtmcconville@mail.utexas.edu (J.T. McConville).

Fig. 1. Diagram of a cross section of the buccal mucosa. The keratinized layer is only present in most rodent models while the human has a non-keratinized buccal mucosa. Adapted from Ref. [39].

propia regions provide mostly mechanical support and no major barrier for penetration of actives [12,27]. The connective tissue also contains the blood vessels that drain into the lingual, facial, and retromandibular veins, which then open into the internal jugular vein [12]. This is one of the main advantages of buccal over oral delivery: absorption through the buccal epithelium avoids the gastrointestinal tract conditions, such as gastric pH, enzyme content, and the first pass effect due to direct absorption into the portal vein. Once a given drug molecule reaches the connective tissue, it may be readily distributed, thus the permeation barrier is across the whole thickness of the stratified epithelium [12].

The existence of membrane-coating granules in the epidermis has been well characterized and it is known to be the precursor of the keratin layer or stratum corneum [18,28]. Even though the existence of approximately 2 μm in diameter cytoplasmic membrane-coating granules in the buccal epithelium has been proven, less is known in terms of their function; however, the permeation barrier is believed to be related to the presence of membrane-coating granules in the buccal mucosa [29,30]. Squier described these membrane-coating granules as organelles containing amorphous material that is extruded into the intercellular space after membrane fusion [29]. More recently, it has been reported that some of these granules also contain lipid lamellae domains organized to some extent [31]. This fact contrasts with the content of the membrane-coating granules in the epidermis, which contains very organized, electron-dense lipid lamellae. Therefore, the intercellular space of the stratified non-keratinized buccal mucosa is filled with a combination of amorphous material presenting some domains where short stack of lipid lamellae can be observed. This important difference in the intercellular space composition is responsible for the difference in permeability between the buccal and keratinized mucosae for exogenous compounds [32].

Although the buccal mucosa is more permeable than keratinized epithelium, the existence of a permeability barrier has been described [33]. It was demonstrated that this barrier is located in the upper one-third to one-quarter of the epithelium layer using horseradish peroxidase, and by following its permeation through the epithelium. After topical application, the horseradish peroxidase only permeated through the first 1–3 cell layers. However, when injected subepithelially, it was found to permeate through

ity barrier is located in the upper region of the epithelium and is correlated with the rich lipid content of this zone. As well as the keratinized epithelium, the intercellular space of the buccal mucosa is rich in lipids, but it is the difference in composition and the absence of the keratin layer that accounts for its permeation characteristics [32,34–37]. The lipid composition in the buccal epithelium has a higher content of phospholipids, cholesterol esters, and glycosylceramides, while the content of ceramides is minimal, compared to the skin and keratinized regions of the oral cavity [32]. This composition results in a higher concentration of polar lipids in the intercellular space [34]. Therefore, it is not only due to the highly organized lipid lamellae found in the keratinized epithelia, but also the nature of the lipid content that accounts for the increased permeation of the buccal mucosa compared to the skin and other keratinized epithelia.

Due to the polar nature of the lipids in the intercellular space, two different domains can be differentiated in the buccal epithelium: the lipophilic domain, corresponding to the cell membranes of the stratified epithelium, and the hydrophilic domain, corresponding to the extruded content from the membrane-coating granules, into the intercellular space. These two domains have led to postulate the existence of different routes of transport through the buccal epithelium, namely the paracellular and the transcellular route [22]. The lipophilic nature of the cell membranes favors the pass of molecules with high log P values across the cells. Similar to the absorption mechanism in the small intestine, it is believed that lipophilic molecules are carried through the cytoplasm [18]. However, there still is a lack of evidence supporting this assumption. The polar nature of the intercellular space favors the penetration of more hydrophilic molecules across a more tortuous and longer path [38–40]. It has been demonstrated that some hydrophilic molecules are subject to carrier-mediated transport through the buccal mucosa [41]. Most of the descriptions of molecules permeating through the buccal epithelium, in the literature, are related to the paracellular route of absorption. In an early study, it was found that tritiated water permeated through the paracellular route [36]. Using light microscopy autoradiography, it has been determined that water, ethanol, cholesterol, and thyrotropin release hormone penetrate through the paracellular route as well [42,43]. More recently, it was demonstrated using confocal laser scanning microscopy that dextrans with 4 and 10 kDa average molecular weight and labeled with fluorescein isothiocyanate permeated through the paracellular route [44,45]. Even though there is no evidence that supports the idea of molecules permeating through the transcellular route, it is important to assess and understand the permeation route in order to determine strategies to enhance the absorption of actives when formulating buccal films.

2. Formulation and manufacture of buccal delivery films

There are many factors in determining the optimum formulation of buccal delivery films, but three major areas have been extensively investigated in the mucoadhesive buccal film literature, namely mucoadhesive properties, permeation enhancement, and controlled release of drugs. Most of the polymers that are used as mucoadhesives are predominantly hydrophilic polymers that will swell and allow for chain interactions with the mucin molecules in the buccal mucosa [6]. Examples of these swellable polymers include hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (SCMC), poly(vinyl pyrrolidone) (PVP), and chitosan; a full list of polymers used in the manufacture

Table 1 shows that polymers from the families of the poly (acrylic acid) (Carbopols) and cellulosic derivatives have been extensively used as mucoadhesives, being part of the so-called first-generation mucoadhesives [46]. These polymers require to be hydrated in order to exhibit their mucoadhesive properties; however, a critical degree of hydration limits the phenomenon [47]. Above this critical value, overhydration occurs, leading to the formation of a slippery mucilage lacking mucoadhesive properties. In an early publication, Guo reported that the use of Carbopol® 934P alone exhibited the triple average peeling strength compared to the one exhibited by HPMC [48]. More recently, Semalty et al. demonstrated using a modified disintegration apparatus that the *in vitro* residence time of films formulated with a combination of Carbopol® 934P and HPMC E15 was almost the double than films containing only HPMC E15 [49]. Moreover, the combined polymers exhibited more resistance to rupture, as demonstrated using the folding endurance test. Another important polymer widely used in the formulation of mucoadhesive films is HPC. In one of the earliest publication on mucoadhesive films, Anders and Merkle showed that the use of different grades of HPC or HEC had superior mucoadhesive properties compared to PVP and poly(vinyl alcohol) (PVA) as film-forming polymers [50]. More recently, it was reported that film formulations, containing different ratios of Carbopol® and HPC, exhibited longer *in vitro* residence times when the concentration of HPC was increased [51].

Natural and semi-natural polymers have also been reported in the literature as mucoadhesives. Chitosan was first introduced in 1994 by Guo for its use in mucoadhesive film formulations [48]. Following Carbopol® and HPMC as polymeric matrices for mucoadhesive films, chitosan exhibited better adhesion than acacia in a peeling test using an Instron 4201. In a more recent study, Shidhaye et al. described the manufacture, permeation, and mucoadhesive properties of chitosan films, containing gelatin and PVP in different proportions, for the buccal delivery of sumatriptan succinate [52]. It was demonstrated that an increase in the chitosan component increased the mucoadhesive strength of films. The authors attributed the increasing concentration of chitosan having the effect of increasing the number of amine groups that can interact with the negative charge groups (carboxyl, sulfate, etc.) which are present on the buccal epithelium surface [53]. Recently, mucoadhesive films have been developed and used as platforms for the oral delivery of nanoparticles [54,55]. Cui et al. reported on the manufacture of carboxylation chitosan-grafted nanoparticles (CCGNs) added to chitosan–ethylenediamine tetraacetic acid (C-EDTA) films with a backing layer of ethyl cellulose (EC) [54]. Films loaded with CCGNs exhibited higher mucoadhesion than that of placebo films. This high mucoadhesion effect was attributed to the high number of carboxyl groups that the CCGNs have, increasing the chance of hydrogen bonding with the mucosa [54].

It is evident that most of the mucoadhesive polymers explored in the literature are hydrophilic or show some of the essential features for mucoadhesion. However, it has been reported that different insoluble Eudragit® grades can exhibit some mucoadhesive properties when used alone [56,57] or in combination with other hydrophilic polymers [58]. Films containing propranolol hydrochloride, Eudragit RS100, and triethyl citrate as a plasticizer exhibited almost three times the mucoadhesion force than that of films prepared with chitosan as the mucoadhesive polymer [56]. The authors proposed that the plasticizer is responsible for the increase in mucoadhesion. However, since the use of a plasticizer is necessary in Eudragit RS100 films, such film formulations may then be suitable for the manufacture of mucoadhesive dosage forms. Salts of soluble polymethacrylate derivatives, namely Eudragit S100 and L100, have been reported to increase mucoadhesion [59]. This

bined with low-swellable properties would allow for better patient compliance. It was demonstrated that, even though the Eudragit S100 and L100 did not exhibit mucoadhesive properties, their sodium and potassium salts performed equally or better than the positive mucoadhesive controls, namely Carbopol® 934P and HPMC [59].

The body of literature that explores different aspects of formulating mucoadhesive buccal films is extensive in terms of polymers used, mucoadhesive properties, and permeation characteristics for formulations. However, only a handful of products have reached the market, and currently, only two products for oral mucosal drug delivery have been successfully commercialized, and one further product has finished a phase 2 clinical study. BioDelivery Sciences International have used their BioErodible MucoAdhesive (BEMA™) technology platform to develop Onsolis™, a fentanyl buccal soluble film indicated to be administered in the buccal mucosa for the management of breakthrough pain in patients with cancer [63]. The formulation contains the mucoadhesive polymers carboxymethyl cellulose, hydroxyethyl cellulose, and polycarbophil, along with a backing layer to direct drug release towards the buccal mucosa. Using the same technology platform, BioDelivery Sciences International have completed a phase 2 clinical study for BEMA™ Buprenorphine with a significant improvement in the primary efficacy endpoint, SPID-8 (sum of pain intensity differences at 8 h), compared to that exhibited by the placebo. The other commercialized film product is Suboxone™ Film, a buprenorphine and naloxone sublingual film. Using a polymeric matrix based on polyethylene oxide and hydroxypropylmethyl cellulose, rapid dissolution and absorption are achieved [64].

The mucoadhesion process and the strategies used to control and enhance drug delivery and permeation will be discussed in later Sections 4 and 5. The following section will discuss the main manufacturing processes involved in making mucoadhesive buccal films, namely film casting and hot-melt extrusion.

2.1. Film casting

The film casting method is undoubtedly the most widely used manufacturing process for making films found in the literature. This is mainly due to the ease of the process and the low cost that the system setup incurs at the research laboratory scale. The process consists of at least six steps: preparation of the casting solution; dearation of the solution; transfer of the appropriate volume of solution into a mold; drying the casting solution; cutting the final dosage form to contain the desired amount of drug; and packaging. During the manufacture of films, particular importance is given to the rheological properties of the solution or suspension, air bubbles entrapped, content uniformity, and residual solvents in the final dosage form [65]. The rheology of the liquid to be casted will determine the drying rates and uniformity in terms of the active content as well as the physical appearance of the films. During the mixing steps of the manufacturing process, air bubbles are inadvertently introduced to the liquid and removal of air is a critical step for homogeneity reasons [2]. Films cast from aerated solutions exhibit an uneven surface and heterogeneous thickness. Another recurrent concern in the manufacture of films for buccal delivery is the presence of organic solvents. The use of organic solvents is normally questioned, not only due to problems related to solvent collection and residual solvents, but also because organic solvents are undesired hazards for the environment and health [65]. However, due to the physicochemical properties of both drug and excipients, many formulations rely on the use of organic solvents, in which case they should be selected from ICH Class 3 solvent list [66]. Even though the current literature on buccal films is

Table 1
Mucoadhesive and film-forming polymers used in the literature.

Mucoadhesive polymer in films	Relevant properties and findings	Use in the literature
Hydroxyethyl cellulose (HEC)	Non-ionic polymer High swelling properties and rapid erosion [109] Low mucoadhesive properties increased by the addition of SCMC [58] Zero-order release kinetics of miconazole [109] and chlorpheniramine [155]	[50,58,109,140,156,155]
Hydroxypropyl cellulose (HPC)	Non-ionic polymer Increased swelling in ethylcellulose/HPC films [137] Moderate mucoadhesive properties [137,157] Zero-order release kinetics of lidocaine [134] and clotrimazole [91] associated with erosion square-root of time release kinetics of lidocaine [87]	[8,9,50,51,81,87,88,90,91,122,123,134,137,154,157–162]
Hydroxypropylmethyl cellulose (HPMC)	Non-ionic polymer Rapid swelling that plateaus [137] Moderate mucoadhesive properties [48,137,157] Initial burst followed by diffusion of nicotine hydrogen tartrate [117]	[4,48,49,57,58,67,74,82,87,107,109,110,113,117,118,137,138,140,156,157, 163–166]
Sodium carboxymethyl cellulose (SCMC)	Anionic polymer High swelling properties that does not plateau [137] High mucoadhesive properties [58,113,137] Zero-order release of miconazole nitrate [109] Diffusion governed release of ibuprofen [113]	[4,11,49,57,58,68,70,71,82,109,110,113,119,137,167]
Poly(vinyl pyrrolidone) (PVP)	Non-ionic polymer [111] As film-forming polymer exhibits non-Fickian release of ketorolac [137] and progesterone Used to tailor the release of propranolol [114] and miconazole [109] High swelling properties [111,112,114] Used as coadjuvant to increase mucoadhesion [76,113]	[50,52,70,76,79,82,109–114,137–140,168]
Poly(vinylalcohol) (PVA)	Non-ionic polymer Moderate swelling [67] and mucoadhesive properties [110,112] Anomalous release of miconazole [109]	[5,50,67,110,112,117,158]
Chitosan	Cationic polymer High to moderate swelling [54,58] and mucoadhesive properties [48,54,124,128,157] Sustained release of miconazole [109]	[10,48,52,54,56,74,79,80,109,111,112,115,124,125,128,156,157,163,164, 169–173]
Alginate, sodium	Anionic polymer Rapid swelling and dissolution [58,169] High mucoadhesive properties [157]	[55,58,69,82,110,157,163,169,165,174]
Agar	Poor and stable swelling properties	[169]
Carrageenan type λ	Poor and stable swelling and moderate mucoadhesive properties	[70]
Acacia	Very poor mucoadhesion	[48]
Guar gum	As an additive, conveyed moderate swelling and good mucoadhesive properties, and anomalous non-Fickian release of miconazole	[156]
Poly-L(lactide-co-glycolide) (PLGA)	Micromatrices in buccal films to control the release of ipriflavone [80]	[80,175]
Polyacrylic acid, Carbopol®	Rapid, high, and stable swelling [107,114,117,137] High mucoadhesive properties [48,157] As a film-forming polymer, conveyed sustained release of buprenorphine [48] Used as an additive to tailor the release of propranolol [114,117]	[3–5,8,11,48,49,51,57,58,69–71,76,107,110,114,117–119, 135–138,157,166,167,170,176–179,165]
Polycarbophil	Non-ionic polymer As an additive, conveyed moderate and stable swelling [70] and high mucoadhesive properties [58,70,81,87,108,180]	[9,58,70,77,78,81,87,108,117,180]
Poly(ethylene oxide)	Non-ionic polymer High mucoadhesion with high molecular weight [86,89] Zero-order release kinetics of clotrimazole [86] and	[86,87,89,94]

Table 1 (*continued*)

Mucoadhesive polymer in films	Relevant properties and findings	Use in the literature
Poly(methacrylates)	Used as film former, exhibited very poor bioadhesive properties and low swelling capability [58,108,114] The salt form has high mucoadhesive properties [59]	[56–59,74,75,77,78,108,113,114,180]

reported. Examples of these research areas are related to the composition of the casting solution [53,96,118,140], drug concentration, the drug addition process, and cast solution rheology [70,71].

Since the early development of medicated films, content uniformity has been a major challenge for the pharmaceutical scientist. Schmidt proposed one of the earliest approaches to increase the drug uniformity of medicated films [72], by stating that the non-uniformity of films is inherent to their monolayered nature. Schmidt proposed a multistep method for the manufacture of multilayered films to overcome the heterogeneity of the monolayered form. However, Yang et al. reported that using the protocol proposed by Schmidt did not render uniform films [73] and went onto say that to overcome the non-uniformity of films, a manufacturing process for orally disintegrating films could be easily adapted for the manufacture of mucoadhesive buccal films. Yang et al. indicated that self-aggregation was one of the main reasons why films usually show poor uniformity, and in particular the drying process was found to be crucial in preventing aggregation or conglomeration of the ingredients of the film formulation [73]. During an inherently long drying process, intermolecular attractive and convective forces are favored, leading to the problem of self-aggregation. In order to avoid non-uniformity, addition of viscous agents such as gel formers or polyhydric alcohols was proposed to alleviate potential self-aggregation [73].

Recently, one of the main challenges in the film casting process, content uniformity along the casting surface, has been addressed [74]. Film characterization in terms of mucoadhesive, mechanical, permeation, and release properties has been widely investigated. However, prior to 2007, few reports pertaining to drug content uniformity can be found [70,86,99–101,141,151,153]. The most common approach to measure the content uniformity is the determination of drug by weight and not by casting area. Perumal et al. postulate that the determination by weight is erroneous because the final dosage form is determined by area instead of weight in the particular case of films. They demonstrate that custom-made silicone-molded trays, with individual casting wells for each dosage form, improved several characteristics significantly, including the content uniformity per casting area unit, mucoadhesive properties, drug release, and thickness uniformity of monopolymeric or multipolymeric films [74]. Even though this approach may solve the problem of uniformity per dosage form, it does not guarantee the uniformity along the dosage unit itself and also imposes limitations on scaling up possibilities.

2.2. Hot-melt extrusion of films

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 [83]. Hot-melt extrusion has been used for the manufacture of controlled-release matrix tablets, pellets, and granules [84], as well as orally disintegrating films [85]. However, only a handful of articles have reported the use of hot-melt extrusion for manufacturing mucoadhesive buccal films. Repka and coworkers have extensively conducted research on the use of hot-melt extru-

blend [86–88,81,9,89]. In an early publication, it was found that even though films containing exclusively HPC could not be obtained, the addition of plasticizers, such as PEG 8000, triethyl citrate, or acetyltributyl citrate, allowed for the manufacture of thin, flexible, and stable HPC films over 6 months [90]. It has also been found that increasing the molecular weight of HPC decreases the release of hot-melt extruded films and allows for zero-order drug release [91]. According to the models applied [92,93], the drug release was solely determined by erosion of the buccal film.

The most recent publications on mucoadhesive extruded buccal films involve the inclusion of Δ^9-tetrahydrocannabinol (THC) and its hemiglutarate ester prodrug (THC-HG) [81,94,89]. Successful mucoadhesive films could be obtained for THC at 120, 160, and 200 °C while still containing at least 94% of the active ingredient. The greatest degradation to cannabinol was observed at 200 °C (1.6%) [81]. For the formulation of the thermally labile prodrug THC-HG, the type of plasticizer was found to be crucial on the post-processing stability [94]. The degradation of the drug in presence of PEG 8000, triacetin, or vitamin E succinate as plasticizers was found to be 1.7%, 1.1%, and 0.4% respectively, the latter being the most efficient plasticizer in preventing degradation at 90 °C and 130 °C [94].

3. Mucoadhesive and mechanical properties of buccal films

3.1. Overview of mucoadhesion

Bioadhesion is the general term describing adhesion between any biological and synthetic surface. Mucoadhesion is a specific term describing the particular interaction of a mucosal membrane with a synthetic surface [95]. The phenomenon of mucoadhesion has been explained by applying any of the five theories of adhesion into the interaction of the dosage form and the biological substrate [13,95,96]. The reader is directed to detailed explanations of the electronic [97], adsorption [98,99], wetting [47,100], diffusion [47,101], and fracture theory [102]; in this article, we briefly summarize theories related to mucoadhesion theory. Since mucoadhesive buccal films include the interaction of a dry polymeric matrix that undergoes hydration, drug release, and sometimes erosion, the phenomenon is very complex. Smart has defined four possible scenarios for the analysis of the mucoadhesion process based on the hydration state of the dosage form and on the amount of mucus layer available for mucoadhesion [103]. Mucoadhesive buccal films can be classified as a "case 3" scenario since they are solid dry substrates that come in contact with a mucosa having thin or discontinuous mucus layers [103]. Relevant to the analysis of the mucoadhesion of polymeric films on the buccal mucosa are the adhesion theories of adsorption and diffusion. The adsorption theory states that the main contributors to the adhesive bond are the inter-polymer interactions, such as hydrogen bonds and van der Waals forces [104]. The diffusion theory assumes that polymeric chains from the solid substrate, i.e. the mucoadhesive film, and the biological substrate, i.e. mucin in the mucosa layer, interdiffuse across the adhesive interface [95]. Important variables in this process are the diffusion coefficient of the polymer into the mucin

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