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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.

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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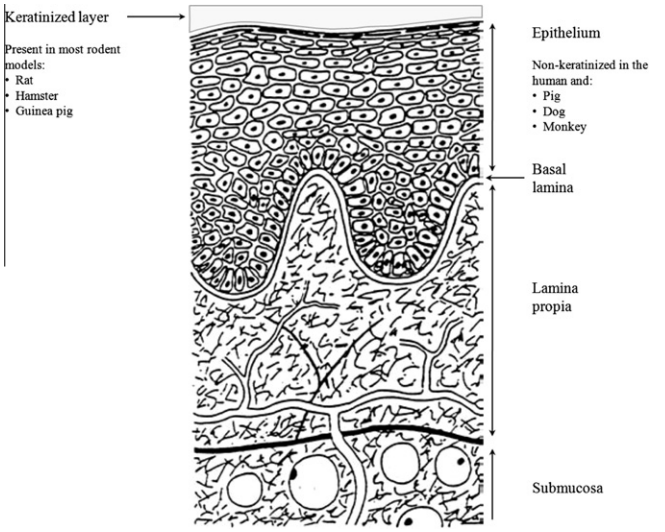

Fig. 1. Diagram of a cross section of the buccal mucosa. The keratinized layer is only present in most rodent models while the human has a non-keratinized buccal mucosa. Adapted from Ref. [39].

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 as deep as the connective tissue and up as far as the membrane-coating granules zone was [33]. This suggested that the permeability 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 of buccal films, with additional descriptions and properties, is depicted in Table 1.

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 study was based on the assumption that ionizable polymers exhibit the best mucoadhesive characteristics [60–62], which combined 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; deareation 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 mostly focused on platforms for specific drugs and diseases, manufacturing and processing parameters have been systematically

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	[50,58,109,140,156,155]
	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]	
Hydroxypropyl cellulose (HPC)	Non-ionic polymer	[8,9,50,51,81,87,88,90,91,122,123,134,137,154,157–162]
	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]	
Hydroxypropylmethyl cellulose (HPMC)	Non-ionic polymer	[4,48,49,57,58,67,74,82,87,107,109,110,113,117,118,137,138,140,156,157,163–166]
	Rapid swelling that plateaus [137] Moderate mucoadhesive properties [48,137,157] Initial burst followed by diffusion of nicotine hydrogen tartrate [117]	
Sodium carboxymethyl cellulose (SCMC)	Anionic polymer	[4,11,49,57,58,68,70,71,82,109,110,113,119,137,167]
	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]	
Poly(vinyl pyrrolidone) (PVP)	Non-ionic polymer [111]	[50,52,70,76,79,82,109–114,137–140,168]
	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]	
Poly(vinylalcohol) (PVA)	Non-ionic polymer	[5,50,67,110,112,117,158]
	Moderate swelling [67] and mucoadhesive properties [110,112] Anomalous release of miconazole [109]	
Chitosan	Cationic polymer	[10,48,52,54,56,74,79,80,109,111,112,115,124,125,128,156,157,163,164,169–173]
	High to moderate swelling [54,58] and mucoadhesive properties [48,54,124,128,157] Sustained release of miconazole [109]	
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]	[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]
	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]	
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 tetrahidrocannabinol [89] associated with erosion of the polymeric matrix	[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 extrusion for the manufacture of mucoadhesive buccal films, evaluating different matrix formers and additives for the processing of the 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 layer and *vice versa*, the contact time, and the molecular chain length and their mobility [105,106].

Most of the mucoadhesive phenomena have two main stages that control the performance of the dosage form: the contact stage and the consolidation stage (Fig. 2) [17,62]. Since mucoadhesive films are dosage forms that are brought in contact with the biological membrane by the patient, the contact stage is initiated by the patient. During the contact process, the film will start dehydrating the mucus gel layer and will itself hydrate, initiating the interpenetration of the polymeric chains into the mucus and *vice versa*. For mucoadhesive films, which usually are designed to remain for prolonged times in contact with the buccal mucosa, a second stage, the consolidation stage, needs to take place in order to maintain this bond. In the consolidation stage, the mucoadhesive strength will be determined by the polymer in the formulation, and how readily the dosage form hydrates upon contact with the mucus gel layer. This process is explained by the dehydration theory, which explains that when a material capable of gelation, such as a mucoadhesive polymer in a buccal film, is brought into contact with an aqueous viscous colloid, water will move until equilibrium is reached between the two layers [62,103]. The strength of the mucoadhesive bond will then be determined by the extent of intermixing that occurs after water migrates and reaches equilibrium.

Mucoadhesive films have been designed to remain in contact with the buccal mucosa for therapeutic purposes for prolonged periods of time. The measurement of the mucoadhesive strength and time of mucoadhesion have been described in parallel with formulation design since the very earliest publications in the field [50,48], this is further discussed in the following section.

3.2. Determination of mucoadhesion

The earliest approaches to measure bioadhesion were indirect and provided an idea of the trend that different formulations followed. In these experiments, instead of measuring the force of adhesion, the studies were focused on determining the time of adhesion or retention time of the dosage form in various models [50,8]. *In vitro* experiments usually consist of attaching a film to a glass plate, or to the sides of a beaker, and a mechanical force is applied either by moving the plate or by stirring the media in the beaker [107,108,78,109]. The first approach is normally done by modifying a standard USP disintegration apparatus [49]. In these experiments, a suitable substrate is attached to the surface of a glass slab, which is connected with the mobile arm of the disintegration apparatus. The film is then allowed to adhere to the substrate, and the time necessary for complete erosion or detachment is recorded as the *in vitro* residence time [109]. Conditions such as the medium composition, pH, temperature, salts addition, or nature of the substrate can be controlled [110] and will modify the results; hence, it is important to report the conditions used to obtain reproducible data [111,112,52,11]. The second approach often used in the literature requires the adhesion of the film into a static surface, normally the side of a beaker, and detachment force is applied by the stirring media [107]. Modifications of this approach include the adhesion of a biological substrate to the side of the beaker, normally a non-keratinized tissue layer such as porcine buccal mucosa [113] to further mimic the physiology of the human buccal epithelium. Again, controlling the composition of the media, temperature, pH, or the nature of the substrate (from either a biological or a synthetic source) will determine the final mucoadhesion or *in vitro* residence time [111,114,69,58].

Even though the measurement of the *in vitro* mucoadhesion or residence time provides information to optimize formulations, it does not elicit the real strength of the mucoadhesive bond. The first article to report on a peeling test for mucoadhesive buccal films was published by Guo in 1994. In these experiments, a load cell is attached to the mobile section of the instrument and force of detachment is obtained and plotted against either distance or time. The mucoadhesion strength of films formulated with Carbopol® 934P, HPMC, chitosan, or acacia gum was expressed as the maximum peeling strength or load using an texture analyzer, such as the Instron 4201 [48]. After this publication, a number of other articles reported on the use of tensile testing instruments, such as the Instron for the measurement of bioadhesive properties. Li et al. were the first to publish the use of a biological membrane as the adhesive substrate for measuring mucoadhesion of buccal films [3]. Freshly excised rabbit buccal mucosa was glued onto a stainless steel platform. Likewise, a buccal film sample was attached to another platform, and following the addition of a drop of water, the film and the substrate were allowed to adhere for a predetermined amount of time. The mucoadhesion strength was measured as the maximum applied force needed in order to detach the film from the substrate [3]. The development of the bench top texture analyzer that allowed for accurate measurement of very small variations, as well as being able to control the contact force and time, increased the number of publications that reported on mucoadhesion and tensile properties of buccal films. The first report on the use of the TA.TX2® texture analyzer (Stable Micro Systems) to measure the mucoadhesion strength of buccal films utilized chicken pouch as the biological membrane upon which the films were allowed to adhere [57]. The instrument measures detachment forces from its mobile arm, which after normalizing is considered as adhesive forces, and the maximum force is normally referred to as mucoadhesive force. The use of this type of texture analyzer for the measurement of mucoadhesion on different dosage forms, such as buccal tablets, had already been published [115,116]. This previous research had focused on the importance of the method variables, which ultimately determine,

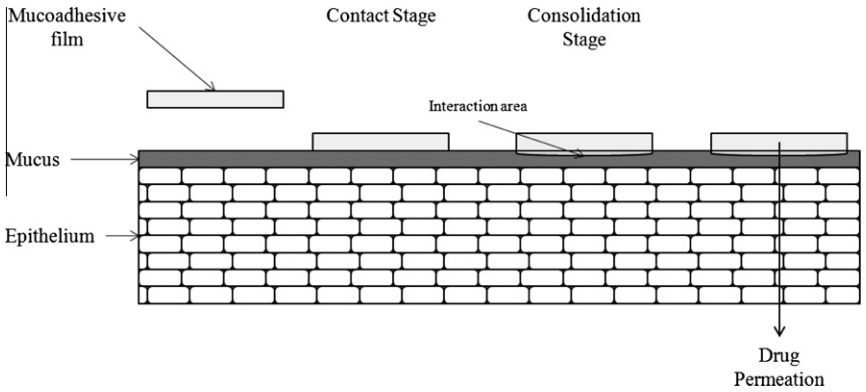

Fig. 2. Contact and consolidation stages of mucoadhesion. Adapted from Ref. [62].

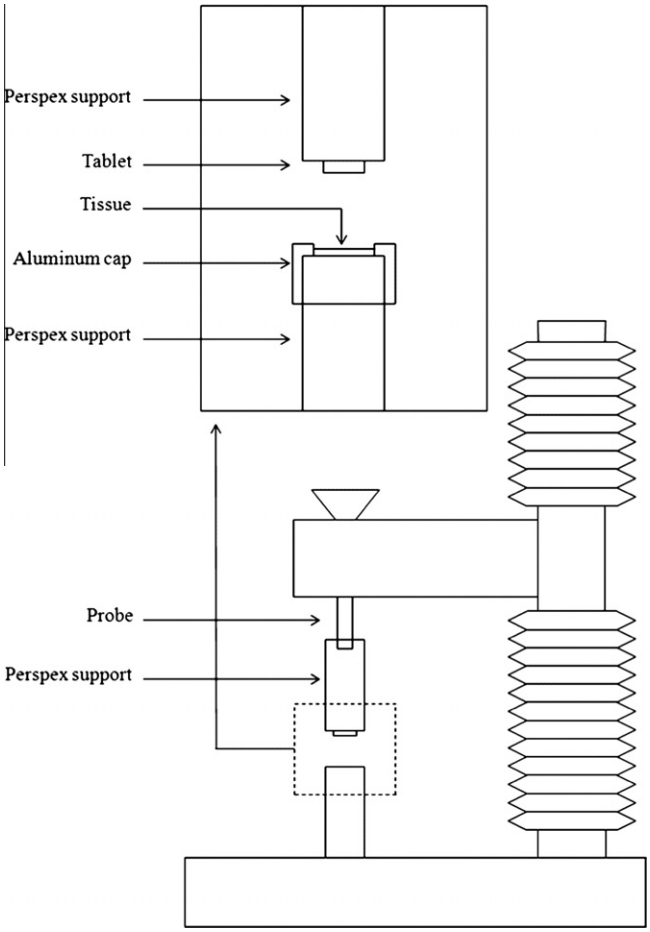

Fig. 3. Mucoadhesion testing apparatus using the texture analyzer TA.XT2, modified from Ref [116].

together with the film and the substrate properties, the value of mucoadhesion strength [116]. Using the instrument depicted in Fig. 3, the authors demonstrate that contact force, contact time, and the speed of probe withdrawal during the mucoadhesion experiment all affect the experimental outcome. The contact time and contact force represent the effort the patient needs to provide in order to bring the dosage form in contact with the buccal mucosal surface and allow for mucoadhesion at the "contact stage" mentioned previously. The contact time was found to be more critical in the affecting the mucoadhesive strength than the contact force. With the exception of an increase in contact time from 10 to 30 s, increasing the contact time significantly increased the measured mucoadhesive strength. However, the authors demonstrated that increasing the contact force from 0.05 N to 0.1 N or 0.5 N to 1.0 N did not significantly increase the mucoadhesive force [116]. Since the development of the mucoadhesive strength test by Wong et al., several modifications have been used to determine this parameter on buccal films [7,70,117,113,56,86,87,81,89]. Measuring the peak force needed to detach a biological substrate attached to a mobile probe, from a wetted mucoadhesive film at various sections of a film cast surface, has been used to demonstrate that the texture analyzer can be used for the determination of mucoadhesion uniformity along the casting area [9]. This is particularly important since the few articles published in the literature account only for the drug content uniformity and do not report any uniformity assessment of film functionality [74]. Some other approaches to measure mucoadhesion include the modification of different mass balance apparatuses to determine the detachment force from the mucoadhesive joint between the buccal film and usually a biological substrate [54,76,55,118,119,114,79,69,82,52]. The reader should note that there is no standardized mucoadhesion test in the literature, which makes the experimental conditions different from paper to paper so extrapolation and comparison of results should be cautious. Moreover, methods that rely on excised tissue are prone to exhibit larger standard deviations compared to *in vitro* conditions.

3.3. Determination of mechanical properties of mucoadhesive films

Besides the important parameter of mucoadhesion strength and residence time of buccal films, the mechanical properties play a crucial role on the physical integrity of the dosage form [4]. Several values can be obtained from a regular stress–strain curve; however, most relevant to the study of buccal films are the tensile strength, the elongation at break, and the elastic modulus, also known as Young's modulus [120,4]. The determination of the mechanical properties of a buccal film is usually based on the ASTM D882 method [121] and measured using instruments such as a texture analyzer. The tensile strength of a film is defined as the resistance of the material to a force tending to tear it apart [52,56,86,90,122–126] and normally identified as the maximum stress in the stress–strain curve and it can be computed in accordance with Eq. (1) [127]:

$$\text{Tensile strength} = \frac{\text{Force at failure}}{\text{Cross-sectional area of the film}} \quad (1)$$

The elongation at break is a measurement of the maximum deformation the film can undergo before tearing apart and is calculated using Eq. (2):

$$\text{Elongation at break} = \frac{\text{Increase in length at break}}{\text{Initial film length}} \times 100 \quad (2)$$

In general, elongation (or strain) will increase with an increasing content of suitable plasticizing agents in a given formulation [129].

Young's modulus is an evaluation of the stiffness or how the film deforms in the elastic region [85]. It is defined in the initial elastic phase of deformation and is obtained from the ratio of applied stress and corresponding strain and can be computed from the slope of the stress–strain curve using Eq. (3):

$$\text{Young's modulus} = \frac{\text{Slope of stress—strain curve}}{\text{Film thickness} \times \text{Cross-head speed}} \quad (3)$$

It has been described that soft and weak polymers have a low tensile strength, low Young's modulus, and low elongation at break, while a soft and strong polymer exhibits a moderate tensile strength, low Young's modulus, and a high elongation at break [130,131]. Desired mechanical properties will vary depending on the formulation goals and the method chosen, but in general, some examples of behaviors obtained from stress–strain curves can be depicted, as shown in Fig. 4 [129].

Tear resistance of a film is normally obtained from stress–strain curves but using very low rates of loading (displacement of 51 mm/min). It is a complex function of the film's ultimate resistance to rupture and is obtained from the maximum stress value and is reported as the correspondent force [2,132].

Finally, another test normally used and reported in the literature is the determination of the folding endurance of the film. The test is performed by repeated folding of the film at the same place until film failure [79]. A maximum of 300 times is sometimes reported as a limit to the test [133], and the value is reported as the number of times the film can be folded prior to rupture.

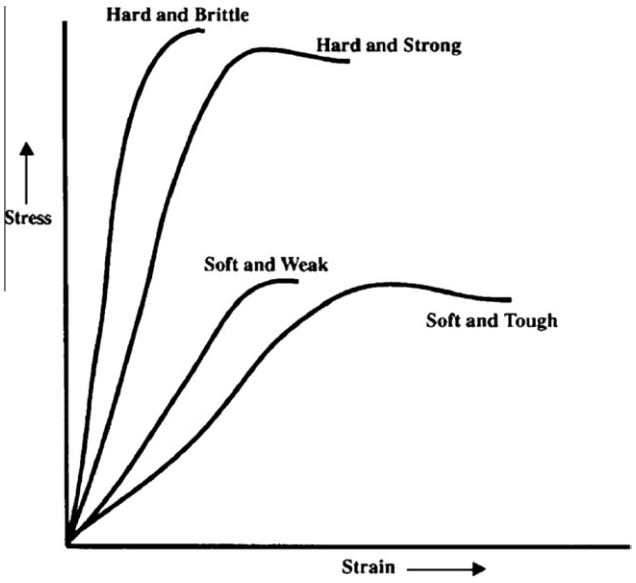

Fig. 4. Examples of behaviors observed in stress–strain curves in polymeric films (from Ref. [129]).

4. Assessment and enhancement of permeation through the buccal mucosa

4.1. Permeation rate determination

Since the early research on the development of mucoadhesive buccal films, drug release from polymeric matrices have been well characterized and reported [134,48,135]. However, these studies were usually conducted using standard or modified dissolution apparatus, thus obtaining only an estimate of the rate of drug release from the film and not penetration rates through the buccal mucosa. Although it is well known that the bioavailability of drugs administered through the buccal route can be highly impacted by the permeation rate through the biological membrane, *in vitro* characterization of permeation properties has not been addressed until recently [7,49,52,68,69,110,114,136–139]. The experimental procedure typically involves the use of a diffusion cell, which can be either vertical, such as a Franz diffusion cell, or horizontally oriented, such as the side-by-side or Ussing diffusion cell. In these cells, a donor compartment is separated from a receptor compartment by a membrane acting as the mucosa model. Conditions such as temperature, composition of the receptor and donor media, pH, cell dimensions, and hydrodynamic conditions are normally controlled in these experiments.

One of the most important components is the membrane that separates the donor from the receptor chambers. It is reported that these membranes may come from either synthetic or biological sources. Synthetic membranes provide a consistent porous path and thus can be used to effectively rank different formulations on the basis of performance [140]. As a substitute for excised animal buccal mucosa, synthetic membranes decrease the large sample to sample variation due to the high structural homogeneity they exhibit, compared to *ex vivo* methods [141,142]. However, their use is limited due to the absence of a stratified non-keratinized epithelium that is present in the buccal mucosa. Depending on the physicochemical characteristics of the drug, permeation of different absorption pathways and interactions with the epithelium will be found, all of which are not applicable in synthetic membranes [142]. Thus, freshly excised mucosa is widely used as the barrier membrane in diffusion studies since it most closely resembles the *in vivo* permeation scenario [27,143]. Consequently, the selection of the animal model is of high importance due to the anatomical differences observed in buccal mucosa among species. Even though rodents are normally the first choice as animal models, their use for buccal delivery purposes is very limited due to their keratinized buccal membrane (Fig. 1). The best model among rodents is the rabbit due to its para-keratinized buccal membrane [144]. In general, large animals exhibit a non-keratinized stratified buccal mucosa, which is more similar to the anatomy of the human and is differentiated mostly in the thickness and permeation properties of the tissue [12]. In terms of availability, thickness, and permeation properties, the swine buccal mucosa appears to be the most suitable animal model, and this is demonstrated widely in the literature [49,52,69,110,139]. Other potential models to study buccal permeation are the dog and the monkey but due to availability, cost, or ethical concerns, they are not commonly used in buccal film research [12]. Another crucial consideration for the permeation test is the tissue storage and isolation before the experiment. This is often overlooked and not reported hindering an adequate interpretation of results. Even though the permeation barrier is believed to be located in the upper one-third or one-quarter of the epithelium, the connective tissue should be removed before the test in order to prevent differences in permeating path, which could translate into large sample to sample variations [143]. The use of chemical, thermal, and enzymatic treatments for removing the connective tissue are not considered to be the methods of choice, as they either have demonstrated to alter permeation or are topics of debate as to their applicability [145,143]. Thus, surgical removal of the connective tissue is the preferred treatment, and it is normally performed right before the permeation experiment by soaking the tissue in phosphate buffer at controlled pH [52,69,136,137]. Integrity of the epithelium before and after the experimental procedure is desired, and it is normally determined by measuring permeation of a non-permeating molecule [146,147] or by light microscopy [136,143].

From a more practical standpoint, the permeability coefficient (P) and the diffusion coefficient (D) are derived from the diffusion process described in one dimension by Fick's second law transformed and simplified to Eq. (4) [143]:

$$F = \frac{P \cdot S}{V_D}\left[t - \frac{h^2}{6D}\right] \tag{4}$$

where the fraction of drug transported (F) is obtained from the relationship between P, the surface area of the tissue (S) (the opening of the diffusion cell), the volume of the donor compound (V_D), time (t), the effective length of buccal mucosa the drug must traverse (h), and D. During a standard diffusion study, P is obtained from the slope of the fraction permeated versus time curve while D is calculated from the x-axis intercept as seen in Eq. (4).

4.2. Permeation enhancers in mucoadhesive buccal films

Due to the limited permeability of the buccal mucosa compared to that of the intestinal epithelium, the use of permeation enhancers has been widely investigated in dosage forms for buccal delivery [18]. Permeation enhancers are pharmaceutical ingredients included in a formulation in order to improve the permeation characteristics of the drug through the target mucosa and are desired to demonstrate null or very limited toxicity or tissue damage [148]. It is known that permeation through the buccal epithelium occurs either by the transcellular or by the paracellular route as previously described, but in general, the overall process can be considered to be governed by passive diffusion [149] and modeled by Fick's first law of diffusion, as shown [18] in Eq. (5):

$$J_{SS} = \frac{D \cdot K}{h} \cdot C_D \tag{5}$$

Table 2
List of permeation enhancers used for buccal delivery.

Permeation enhancer	Proposed mechanism of action	Preferred route enhanced	Examples
Surfactants	Lipid extraction from the mucosa	Paracellular	Sodium dodecyl sulfate [181] Sodium lauryl sulfate [182]
Bile salts	Lipid extraction from the mucosa	Paracellular	Sodium glycocholate [45,150] Sodium taurocholate, sodium glycodeoxycholate, and sodium taurodeoxycholate [45] Sodium deoxycholate [68]
Fatty acids	Increase fluidity of intercellular lipids	Paracellular[a]	Oleic acid [136,183,184] Eicosapentaenoic acid and or docosahexaenoic acid [184]
Ethanol	Disrupt arrangement of intercellular lipids	Paracellular[a]	[185,186]
Chitosan	Increase retention time of drug in contact with mucosa and disruption of intercellular lipid organization	Paracellular[a]	

[a] No definitive evidence.

where the steady state flux (J_{ss}) is determined by D of the drug within the buccal mucosa, the partition coefficient (K) of the drug between the buccal mucosa and the donor chamber solution, the concentration of drug in the donor compartment (C_D), and h. Most of the permeation enhancers will alter the mucosa or the permeating molecule in such a way that D or K or both can be enhanced. Based on the physicochemical characteristics of the drugs, delivery using different permeation enhancers will be suitable. As seen in Table 2, permeation enhancers used in the buccal mucosa favor the paracellular route of drug absorption, or it has been suggested that they work in such a way. Even though many permeation enhancers have been described to be effective in the buccal mucosa [150–153], few buccal film formulations have studied the inclusion of such agents in their compositions. One of the earliest studies with penetration enhancers in the formulation included the use of glycyrrhizic acid in lidocaine containing HPC mucoadhesive buccal films. In this study, the authors found a direct relationship between an increase in glycyrrhizic acid content and the penetration rate through freshly excised hamster buccal epithelium. Thus, in this example, a permeation enhancement effect of glycyrrhizic acid in the presence of the active ingredient was seen through the keratinized rodent epithelium [154]. In a previous report, same authors hypothesized that the effect of glycyrrhizic acid is due to the formation of an amorphous state of lidocaine in the dosage form [134]. In another study, oleic acid and propylene glycol monolaurate were used as penetration enhancers for lidocaine hydrochloride in mucoadhesive buccal films made of Carbopol® 971P. The permeation studies for these lidocaine films were performed using Franz diffusion cells and utilizing porcine buccal mucosa as the model membrane. After demonstrating that oleic acid as the penetration additive exhibited the best enhancing characteristics, the authors performed *in vivo* studies and proved that incorporation of oleic acid did not produce any discernible redness or irritation of the buccal mucosa after 8 h of exposure [136]. More recently, films formulated with chitosan and PVP K30 as mucoadhesives with different permeation enhancers were tested to determine the highest increase in diffusion of sumatriptan succinate through porcine buccal mucosa [52]. It was determined that the use of dimethyl sulfoxide in the highest concentration studied (3% w/w) exhibited the best enhancing characteristics compared to transcutol 5% w/w or polysorbate-80 1% w/w. The addition of penetration enhancers did not modify the physicochemical properties of their formulations, making them ideal for the manufacture of improved mucoadhesive buccal films.

5. Conclusion

The buccal mucosa is a promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes, or due to a substantial hepatic first pass effect. It can also be an alternative to skin, pulmonary, or nasal delivery. The physiology of the buccal mucosa allows for the penetration of active substances and due to its rapid cellular turnover and recovery, the use of penetration enhancers is possible. Moreover, recent publications have proved that the addition of permeation enhancers on buccal films did not hinder the manufacturing capability nor imposed mucosal irritation or toxicity. In the laboratory scale, film casting remains as the manufacturing process of choice. Nonetheless, hot-melt extrusion has been successfully explored as a method for obtaining mucoadhesive buccal films for the delivery of THC through the buccal mucosa. Many possibilities remain in the design of buccal films, including their recent application as platforms for the delivery of nanoparticles; however, the manufacture of patient safe and friendly dosage forms while improving technologies will keep challenging the pharmaceutical scientist.

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