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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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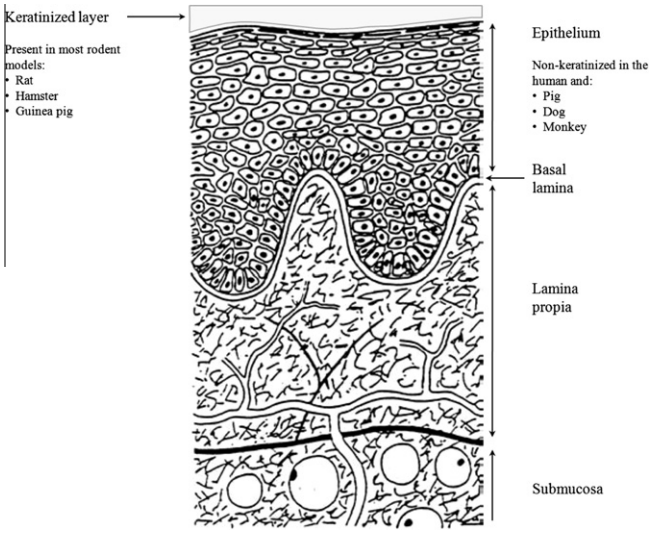

Fig. 1. Diagram of a cross section of the buccal mucosa. The keratinized layer is only present in most rodent models while the human has a non-keratinized buccal mucosa. Adapted from Ref. [39].

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

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 of buccal films, with additional descriptions and properties, is

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