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Review Article

POLYMERIC PLATFORM FOR MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage form. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Furthermore, films have improved patient compliance due to their small size and reduce thickness, compared for example 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. This paper aims to review the development in the buccal adhesive drug delivery system to provide basic principles to the researchers, which will be useful to circumvent the difficulties associated with the formulation design.

Keywords: Review, Buccal drug delivery, Mucoadhesive

INTRODUCTION

The buccal route of administration has a number of advantages including bypass the gastrointestinal tract and the hepatic first pass effect. Mucoadhesive films are retentive dosage form and release drug directly into biological structure. Films as dosage forms have gained relevance in the pharmaceutical arena as novel, patient friendly, convenient products[1]. More recently, orally disintegrating films have come to light, with improved mechanical properties. This translate, into a less friable dosage form compared to most commercialized orally disintegrating tablets, which usually require special packaging. Mucoadesive Buccal films share some of these advantages and more. Due to small size and thickness, they have improved patient compliance, compared to tablet. Moreover, since mucoadhesion implies attachment to the Buccal mucosa, films can be formulated to exhibit a systemic or local action. Many mucoadhesive buccal films have been formulated to release drug locally in order to treat fungal infection in the oral cavity such as oral candidiasis[2]. 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 later case, it can provide controlled release via gastrointestinal tract administration. Alternatively, films can be formulated to release the drug towards the buccal mucosa[3]. Films releasing drug towards the buccal mucosa exhibit the advantages of avoiding the first pass effect by directing absorption through the cheek. Previously, many articles have reviewed the development of mucoadhesive buccal system in global terms, or their specific attributes such as permeation enhancers or mucoadhesive polymers[4].

Buccal mucosal structure and its properties:

Buccal mucosa composed of several layers of different cells (fig:1). The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 50% cells layers thick. Lining epithelium of buccal mucosa is that has thickness of approximately 500-600 μ and surface area 50 cm^2. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer[5]. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. Lipid analysis of buccal tissue shows the presence of phospholipids 76%, glucosphingolipid 23% and ceramide 0.72%.

The primary function of buccal epithelium is the protection of the underlying tissues. In nonkeratinized regions. Lipid-based permeability barriers in the outer epithelial layer protect the underlying tissues against fluid loss and entry of potentially harmful environment agent such as antigens, carcinogens, microbial toxins and enzymes from food and beverages.

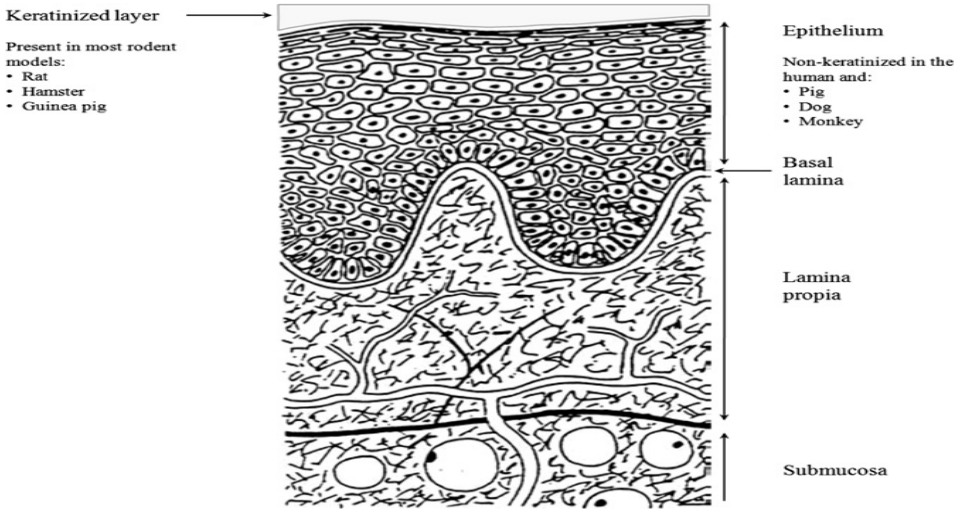

Fig-1: Structure of Buccal Mucosa

Absorption Pathway:

Studies with microscopically visible traces such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the inter-cellular spaces and that there is a barrier to penetration as a result of modification to the intercellular substances in the superficial layers. However, rate of penetration varies depending on the physicochemical properties of the molecules and the type of tissue being traversed. This has led to the suggestion that material uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusant[6].

The flux of the drug through membrane under sink condition for paracellular route can be written as:

$Jp = D_p$ / h_p x C_d

Where D_p is diffusion coefficient of the permeate in the intercellular spaces, h_p is the path length of the paracellular route, is the area fraction of the paracellular route and C_d is the donor drug concentration.

Similarly, flux of drug through the membrane under sink condition for transcellular route can be as:

$Jc = (1-$) $D_c K_c / h_c$ x C_d

Where K_c is partition coefficient between lipophilic cell membrane and the aqueous phase, D_c is the diffusion coefficient of the drug in the transcellular spaces and h_c is the path length of the transcellular route[7].

The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and decreases with increase of pH. However, the pH dependency that is evident in absorption of ionizable compounds reflect their partitioning into the epithelium cell membrane, so it is likely that such compounds will tend to penetrate transcellularly. Weak acids and weak bases are subjected to pH-dependent ionization. It is presumed that ionozed species penetrate poorly through the oral mucosa compared with non-ionized species. An increase in the amount of non-ionized drug is likely to increase the permeability of the drug across an epithelial barrier, and this may be achieved by a change of pH of the drug delivery system. It has been reported that pH has effect on the buccal permeation of drug through oral mucosa. The diffusion of drugs across buccal mucosa was not related to their degree of ionization as calculated from the Henderson-Hasselbalch equation and thus it is not helpful in the prediction of membrane diffusion of weak acids and weak basic drugs[8].

Barriers to penetration across buccal mucosa:

Membrane coating granules: The membrane coating granules found in non-keratinizing epithelia are spherical in shape, membrane bounded and measured about 0.2 μm in diameter. Such granules have been observed in a variety of other human nonkeratinized epithelia, including uterine cervix and esophagus.

Basement membrane: Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

Mucus: The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 μm to 300 μm. Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems[9]. At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus molecules are able to join together to make polymers or an extended three-dimensional network. Different types of mucus are produced, for example G, L, S, P and F mucus, which form different network of gels. Other substances such as ions, protein chains, and enzymes are also able to modify the interaction of the mucus molecules and, as a consequence, their biophysical properties[10]. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core. Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic tomucus. Mucins contain approximately 70–80% carbohydrate, 12–25% protein and up to 5% ester sulphate. The dense sugar coating of mucins gives them considerable water-holding capacity and also makes them resistant to proteolysis, which may be important in maintaining mucosal barriers. Mucins are secreted as massive aggregates by prostaglandins with molecular masses of roughly 1 to 10 million Da. Within these aggregates, monomers are linked to one another mostly by noncovalent interactions, although intermolecular disulphide bonds also play a role in this process. Oligosaccharide side chains contain an average of about 8–10 monosaccharide residues of five different types namely L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and sialic acid. Amino acids present are serine, threonine and proline[11]. Because of the presence of sialic acids and ester sulfates, mucus is negatively charged at physiological salivary pH of 5.8–7.4.

Saliva: The mucosal surface has a salivary coating estimated to be 70 μm thick, which act as unstirred layer. Within the saliva there is a high molecular weight mucin named MG1 that can bind to the surface of the oral mucosa so as to maintain hydration, provide lubrication, concentrate protective molecules such as secretory immunoglobulins, and limit the attachment of microorganisms. Several independent lines of evidence suggest that saliva and salivary mucin contribute to the barrier properties of oral mucosa. The major salivary glands consist of lobules of cells that secrete saliva; parotids through salivary ducts near the upper teeth, submandibular under the tongue, and the sublingual through many ducts in the floor of the mouth. Besides these glands, there are 600–1000 tiny glands called minor salivary glands located in the lips, inner cheek area (buccal mucosa), and extensively in other linings of the mouth and throat. Total output from the major and minor salivary glands is termed as whole saliva, which at normal conditions has flow rate of 1–2 ml/min[12]. Saliva is composed of 99.5% water in addition to proteins, glycoproteins and electrolytes. It is high in potassium (7×plasma), bicarbonate (3×plasma), calcium, phosphorous, chloride, thiocyanate and urea and low in sodium(1/10×plasma). Saliva serves multiple important functions. It moistens the mouth, initiates digestion and protects the teeth from decay. It also controls bacterial flora of the oral cavity. Because saliva is high in calcium and phosphate, it plays a role in mineralization of new teeth repair and precarious enamel lesions. It protects the teeth by forming “protective pellicle”. This signifies a saliva protein coat on the teeth, which contains antibacterial compounds. Thus, problems with the salivary glands generally result in rampant dental caries. A constant flowing down of saliva within the oral cavity makes it very difficult for drugs to be retained for a significant amount of time in order to facilitate absorption in this site. Permeabilities between different regions of the oral cavity vary greatly because of the diverse structures and functions. In general, the permeability is based on the relative thickness and degree of keratinization of these tissues in the order of sublingual>buccal> palatal. The permeability of the buccal mucosa was estimated to be 4–4000 times greater than that of the skin[13].

Mucoadhesion

The term “Mucoadhesion” describes the adhesion of material to biological membrane. Adhesion of bioadhesive drug delivery devices to the mucosal tissues offers the possibility of creating an intimate

and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration[14].

Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanisms involved. These theories include mechanical-interlocking, electrostatic, diffusion–interpenetration, adsorption and fracture processes. These numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories.

The wettability theory:

The wettability theory is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the ''spreadability" of the drug delivery system across the biological substrate. This theory postulates that the adhesive component penetrates surface irregularities, hardens and anchors itself to the surface. The adhesive performance of such elastoviscous liquids may be defined using wettability and spreadability; critical parameters that can be determined from solid surface contact angle measurements. This process defines the energy required to counter the surface tension at the interface between the two materials allowing for a good mucoadhesive spreading and coverage of the biological substrate. Therefore the contact angle (Ø), which may be easily determined experimentally, is related to interfacial tension (c), of both components using

$\acute{y}_{SG} = \acute{y}_{SL} + \acute{y}_{LG} \cos Ø$

$S = \acute{y}_{SG} - (\acute{y}_{SL} - \acute{y}_{LG})$

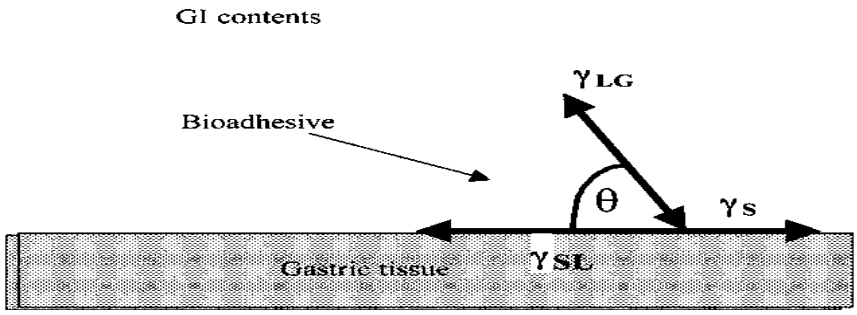

Fig. 2: Wettability Theory : Angle between tissue and Polymer solution

where $\acute{y}_{LG}$ is liquid–gas surface tension, $\acute{y}_{SL}$ is solid–liquid surface tension and $\acute{y}_{SG}$ is solid–gas surface tension[15].

The electronic theory:

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer.

The fracture theory:

According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This ''fracture theory" relates the force for polymer detachment from the mucus to the strength of their adhesive bond. The work fracture has been found to be greater when the polymer network strands are longer or if the degree of cross-linking within such as system is reduced. This theory allows the determination of fracture strength (r) following the separation of two surfaces via its relationship to Young's modulus of elasticity (E), the fracture energy (e) and the critical crack length (L) through the following equation[16]:

$$r = (E \times e / L)^{½}$$

The adsorption theory:

In this instance, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. Secondary bonds arise mainly due to vander Waals forces, hydrophobic interactions and hydrogen bonding. While these interactions require less energy to 'break' they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds[17].

The diffusion-interlocking theory:

This theory proposes the time-dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer. This is a two-way diffusion process with penetration rate being dependent upon the diffusion coefficients of both interacting polymers. Although there are many factors involved in such processes, the fundamental properties that significantly influence this inter-movement are molecular weight, cross-linking density, chain mobility/flexibility and expansion capacity of both networks. Furthermore, temperature also has been noted as important environmental factor for this process. While it is acknowledged that longer polymer chains may diffuse, interpenetrate and ultimately entangle to a greater extent with surface mucus, it should be recognised that a critical chain length of at least 100,000 Da is necessary to obtain interpenetration and molecular entanglement. The time at which maximum adhesion occurs between two substrates during interpenetration has been supported by experimental evidence in recent studies using FTIR and rheological techniques, and may be determined using the depth of interpenetration (L), and the diffusion coefficient (Db)[18]:

$$t = L^2 / Db$$

Mucoadhesive Polymers:

Most of the mucoadhesive materials are either synthetic or natural hydrophilic or water insoluble polymers and are capable of forming numerous hydrogen bonds because of presence of carboxyl, sulphate or hydroxyl functional groups[19].

Ideal Properties of mucoadhesive polymers:

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.

- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Table 1: Properties of some mucoadhesive polymers

Mucoadhesive Polymers	Properties of polymer
Chitosan[20,21]	Cationic polymer, High to moderate swelling and mucoadhesive properties
Alginate Sodium[22,23]	Anionic polymer, Rapid swelling and dissolution, High mucoadhesive properties
Polyvinyl alcohol[24,25]	Non-ionic polymer, Moderate swelling and mucoadhesive properties
Poly vinyl Pyrrolidone[26,27]	Non-ionic polymer, As film-forming polymer, High swelling properties Used as coadjuvant to increase mucoadhesion
Agar[28]	Poor and stable swelling properties
Acacia[29]	Very poor mucoadhesion
Guar gum[30]	As an additive, conveyed moderate swelling and good mucoadhesive properties
Carrageenan (λ)[31]	Poor and stable swelling and moderate mucoadhesive properties
Sodium carboxymethyl Cellulose (SCMC)[32,33]	Anionic polymer, High swelling properties that does not plateau, High mucoadhesive properties
Hydroxyethyl Cellulose (HEC)[34,35]	Non-ionic polymer, High swelling properties and rapid erosion, Low mucoadhesive properties increased by the addition of SCMC
Hydroxypropyl cellulose (HPC)[36,37]	Non-ionic polymer, Increased swelling in ethylcellulose/HPC films, Moderate mucoadhesive properties
Hydroxypropylmethyl cellulose (HPMC)[38,39]	Non-ionic polymer, Rapid swelling that plateaus, Moderate mucoadhesive properties
Poly ethylene oxide[40,41]	Non-ionic polymer, High mucoadhesion with high molecular weight
Xantham gum[42]	Anionic polymer, High swelling properties and high mucoadhesive properties

Design of buccal delivery system:

An ideal buccal adhesive system must have the following properties:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in an unidirectional way toward the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

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. 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 or in combination with other hydrophilic polymers. 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. 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. 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. 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. There are following methods i.e film casting and hot-melt extrusion for the manufacturing of mucoadhesive buccal films[43].

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. 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. 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. Since the early development of medicated films, content uniformity has been a major challenge for the pharmaceutical scientist. Some scientists proposed one of the earliest approaches to increase the drug uniformity of medicated films, by stating that the nonuniformity of films is inherent to their monolayered nature. They proposed a multistep method for the manufacture of multilayered films to overcome the heterogeneity of the monolayered form. 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. Recently, one of the main challenges in the film casting process, content uniformity along the casting surface, has been addressed. Film characterization in terms of mucoadhesive, mechanical, permeation, and release properties has been widely investigated. The most common approach to measure the content uniformity is the determination of drug by weight and not by casting area[44,45].

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. Hot-melt extrusion has been used for the manufacture of controlled-release matrix tablets, pellets, and granules, as well as orally disintegrating films. However, only a handful of articles have reported the use of hot-melt extrusion for manufacturing mucoadhesive buccal films. 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. 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. According to the models applied, 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 D9-tetrahydrocannabinol (THC) and its hemiglutarate ester prodrug (THC-HG). 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%). For the formulation of the thermally labile prodrug THC-HG, the type of plasticizer was found to be crucial on the post-processing stability. 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.[46,47]

CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. From both a financial and global healthcare perspective, finding ways to administer injectable medications is costly and some time leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailabilities are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated.

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. 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 drugs 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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