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Oral Bioadhesive Drug Delivery Systems

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ABSTRACT The oral mucosal cavity is a feasible, safe, and very attractive site for drug delivery with good acceptance by users. The mucosa is relatively permeable and robust, shows short recovery times after stress or damage, is tolerant to potential allergens, and has a rich blood supply. Moreover, oral mucosal drug delivery bypasses the first-pass effect and avoids presystemic elimination in the gastrointestinal tract. Bioadhesive systems provide intimate contact between a dosage form and the absorbing tissue, which may result in high concentration in a local area and hence high drug flux through the absorbing tissue. The efficacy of oral bioadhesive drug delivery systems is affected by the biological environment and the properties of the polymer and the drug. In the present paper, we review systematically some relevant citations regarding the environment, strategies for oral drug delivery and evaluation, and utilization of the main polymers.

KEYWORDS Bioadhesion, Oral mucosa, Oral cavity, Buccal, Drug delivery systems

INTRODUCTION

Among the various routes of drug delivery, the peroral one is perhaps the most preferred by patient and clinician alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal tract. These disadvantages may limit or prevent the oral administration of certain classes of drugs, especially peptides and proteins, except when they are inserted in colon-specific delivery systems (Shojaei, 1998). These limitations motivated the exploration of other mucosae as potential release and drug absorption sites. Transmucosal routes of drug delivery (e.g., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first-pass effect and avoidance of presystemic elimination within the gastrointestinal tract (Chidambaram & Srivatsava, 1995; Gandhi & Robinson, 1994).

Many factors make the oral mucosal cavity a very attractive and feasible site for drug delivery (Varshosaz & Dehghan, 2002; Walker et al., 2002). The mucosa is relatively permeable with a rich blood supply, it is robust and shows

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short recovery times after stress or damage, and the virtual lack of Langerhans cells makes it tolerant to potential allergens (Shojaei, 1998). Drug delivery across the buccal epithelium bypasses the first-pass effect, avoids presystemic metabolism in the gastrointestinal tract, and offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity (Wong et al., 1999a). The mouth is an accessible site for placement of devices (Needleman & Smales, 1995) and is well accepted by users.

OVERVIEW OF THE ORAL CAVITY

Structure

The oral cavity has a relatively small surface area (approximately 50 cm^2) (Woodley, 2001). The oral mucosa is composed of stratified squamous epithelium, an outermost layer similar to that found in the rest of the body. It has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium (Gandhi & Robinson, 1988; Woodley, 2001). The turnover time for the buccal epithelium has been estimated at 5–6 days, a time probably representative of the oral mucosa as a whole (Harris & Robinson, 1992). The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500–800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm (Shojaei, 1998).

The composition of the epithelium also varies depending on the site in the oral cavity. It may be keratinized, para-keratinized, or nonkeratinized (Chidambaram & Srivatsava, 1995). The mucosa of areas subject to mechanical stress (the gingivae and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual and buccal regions, however, is not keratinized (Harris & Robinson, 1992). The keratinized epithelia contain neutral lipids like ceramides and acylceramides, which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelium, do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia (Shojaei, 1998).

Various appendages are situated in or below the lamina-propria. These comprise teeth, the salivary gland ducts, and occasionally, sebaceous glands. These structures communicate with the outer environment and interrupt the otherwise intact surface, providing a route for substances unable to penetrate the epithelium proper, thus forming shunts or parallel diffusion pathways (Chidambaram & Srivatsava, 1995).

Permeability

The connective tissue of the oral mucosa limits the permeability of polar substances, although it may tend to permit the diffusion of nonpolar drug compounds. While a rapid absorption of drugs from the oral cavity has been ascribed to the rich vascular supply of the oral mucosa, it would appear that the blood supply, unless it is drastically reduced, is not normally a significant factor. The oral mucosa provides a protective covering for the underlying tissue, acting as a barrier against microorganisms and toxins (Chidambaram & Srivatsava, 1995).

The oral mucosa in general is a somewhat leaky epithelium intermediate between that of the epidermis and intestinal mucosa, whose estimated permeability is 4–4000 times greater than that of the skin. In general, the permeability of the oral mucosa decreases in the order of sublingual greater than buccal, and buccal greater than palatal (Shojaei, 1998).

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called "membrane coating granules" (MCG) (Gandhi & Robinson, 1994). In both keratinized and nonkeratinized epithelia, the limit of penetration coincides with the level, where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. The components of the MCGs in keratinized and nonkeratinized epithelia are different. The MCGs of keratinized epithelium are composed of lamellar lipid stacks represented by sphingomyelin, glucosylceramides, ceramides, and other nonpolar lipids. On the other hand, the

nonkeratinized epithelium contains MCGs that are nonlamellar; the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids. In addition to the MCGs, the basement membrane may present some resistance to permeation as well; however, the outer epithelium is still considered to be the rate-limiting structure in mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules, but it may limit the passage of certain particles such as immune complexes (Shojaei, 1998).

The intercellular route through oral epithelium is essentially an aqueous channel, especially in the deeper cell layers. The oral mucosa shares with the gut the ability to maintain a moist surface, one of the characteristics of any mucous membrane. As far as permeability is concerned, this is both a strength and weakness because, while saliva components may contribute to barrier function, the accompanying hydration may increase permeability. Substances can cross cells by endocytosis, by active transport, and by diffusion through the intercellular spaces. In endocytosis, a large number of different cell types are capable of taking up solid particles (phagocytosis) or fluids (pinocytosis) from the outer environment by engulfing the material in membranous vesicles. The processes, referred to in general as endocytosis, affords a means of transporting materials across the cell membrane or transferring material across the whole cell. Cells of the oral epithelium are capable of taking up materials by endocytosis, particularly in the basal and prickle layers (Chidambaram & Srivatsava, 1995).

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the main components of which are complexes made up of proteins and carbohydrates. These complexes may be loose or some may be attached to certain regions on the cell surfaces. This matrix may actually play a role in cell–cell adhesion, also acting as a lubricant, allowing cells to move relative to one another. Similarly, mucus generally plays a critical role in the bioadhesion of mucoadhesive drug delivery systems (Ahuja et al., 1997). In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus-secreting cells like goblet cells, whereas in the oral mucosae, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands (Shojaei, 1998). At physiological pH, the mucus network carries a negative charge (due to the sialic acid and sulphate residues), which plays a role in mucoadhesion. At this pH, mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer (Gandhi & Robinson, 1988).

Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralization of the tooth enamel after eruption and contributes to remineralization of the enamel in the early stages of dental caries (Edgar, 1992; Jones et al., 2000). Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate, which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation (Edgar, 1992). The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase, leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral drug delivery systems is this water-rich environment of the oral cavity (Shojaei, 1998).

Additionally, proteolytic activities of endo- and exopeptidases (aminopeptidases and carboxypeptidases) have been identified in buccal tissue homogenates (Walker et al., 2002). A number of peptide drugs have been shown to be degraded in buccal tissue homogenates including enkephalin analogues (Kashi & Lee, 1986), calcitonin (Nakada et al., 1987), insulin, proinsulin (Yamamoto et al., 1990), substance P (Lee & Yamamoto, 1990), and thyrotropin releasing hormone (Dowty et al., 1992). However, as the peptidase activity of cytosol and the membrane cannot be resolved in tissue homogenates, the relevance of these activities during peptide buccal transport is uncertain (Walker et al., 2002). Particularly, it is believed that peptides are transported between the epithelial cells and therefore,

the cytosolic peptidase activity may not be in contact with the peptide during its transport (Rathbone & Tucker, 1993).

Recent studies have contributed to differentiate the cytosolic enzymes of those present in the membrane. The activity of aminopeptidases, using Leu-enkephalin as substrate, was observed on the surface of the intact buccal mucosa excised from pig (Walker et al., 2002). These authors also demonstrated that the insulin and insulin B-chain were not hydrolyzed. Aminopeptidases can only act on insulin B-chain after the initial cleavage by an endopeptidase (Song et al., 1986), while the insulin is not a substrate for aminopeptidases (Stephenson & Kenny, 1988). These results support the hypothesis of the aminopeptidases presence and absence of endopeptidases and carboxypeptidases on the surface of the intact buccal mucosa. The insulin stability in contact with the intact buccal mucosa (Walker et al., 2002), its fast hydrolysis in contact with buccal tissue homogenate, without a serine protease inhibitor aprotinin (Yamamoto et al., 1990), and the fact that the in vivo coadministration of the enzyme inhibitor aprotinin with insulin did not improve the bioavailability of insulin across the rat buccal mucosa (Aungst & Rogers, 1988), suggest that the insulin hydrolytic activity, observed on the tissue homogenate, was owed to the cytosolic enzymatic activity.

The possibility of peptides absorption through the intercellular route, the absence of endopeptidases and carboxypeptidases activity in the buccal mucosa surface, and the possibility of use of specific enzymatic inhibitors, pleads in favor of the oral cavity as a promising site for the administration of specific drugs. However, a substantial sum of research is still necessary to demonstrate the rate and the extension of the degradation and of the absorption of each candidate drug to be administrated in this site.

Oral Mucosal Routes of Drug Absorption

The cellular structure of the oral mucosa suggests that there are two permeability barriers (Zhang & Robinson, 1996). Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment. On the other hand, the cell membrane is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces act as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Considering the coexistence of the hydrophilic and lipophilic regions in the oral mucosa, drug transport may involve a combination of the paracellular and the transcellular routes. All compounds can use these two routes simultaneously, except that one route is usually preferred over the other depending on the physicochemical properties of the diffusant.

ORAL MUCOSA AS A SITE FOR DRUG DELIVERY

Within the oral mucosal cavity, drug delivery is classified into three categories: 1) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, 2) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and 3) local delivery, which is drug delivery into the oral cavity (Shojaei, 1998).

The selection of one category over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailability seen with sublingual administration (Harris & Robinson, 1992).

Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches, bacterial and fungal infections, aphthae and dental stomatitis, and the facilitation of tooth movement with the use of prostaglandins (Bottenberg et al., 2000; Jones et al., 2000; Needleman & Smales, 1995; Repka et al., 2003; Shojaei, 1998; Vivien-Castioni et al., 2000).

Moreover, there is intra-periodontal pocket drug delivery, which is a special category of local delivery where the drug delivery happens in a specific site, within the periodontal pocket (Medlicott et al., 1994), being generally used for treatment of periodontitis (Soskolone & Freidman, 1996). Periodontitis is an

inflammatory and infectious disease resulting in the destruction of the supporting structures of the teeth (the periodontal ligament and the alveolar bone). It results in the formation of pockets between the soft tissue of the gingiva (gum) and the tooth, and can eventually cause tooth loss (Jones et al., 2000). Currently, the treatment of periodontal disease, aimed at arresting the progression of the destructive process and preventing recurrence after treatment, is mainly through mechanical cleaning of the tooth surface to remove bacterial plaque and calculus. The potential side effects of the administration of systemic antibiotics and the inability of antiseptic mouthwashes to penetrate the periodontal pocket have fueled interest in the sustained delivery of therapeutic agents within the periodontal pocket, thus ensuring a high, effective concentration of the antimicrobial agent at the site of infection. Consequently, studies on the release of antimicrobial agents, e.g., chlorhexidine, tetracycline, or metronidazole, from several polymeric systems, and the evaluation of their clinical effects have been reported. It has been suggested that mucosa adhesive polymers might be useful for periodontal pocket therapy (Newman, 1992). These problems may be primarily overcome by antimicrobial-containing formulations that are easily introduced into the periodontal pocket (Soskolone & Freidman, 1996).

Intra-periodontal pocket drug delivery systems can be bioadhesives, which interact with the mucin-coated epithelial and tooth surfaces by means of mucoadhesion, and/or produce a sustained effect by virtue of being viscous, ensuring the formulation retention within the pocket (Jones et al., 2000; Medlicott et al., 1994).

STRATEGIES FOR ORAL MUCOSAL DRUG DELIVERY

Novel oral dosage forms consist mainly of sustained release systems for oral mucosal delivery intended to release the drug within a defined period of time. The different formulations for sustained oral release can be grouped into two categories: 1) adhesive systems and 2) chewing gums (Chidambaram & Srivatsava, 1995). An adhesive system provides intimate contact between a dosage form and the absorbing tissue, which may result in high concentration in a local area and hence, high drug flux through the absorbing tissue (Ahuja et al., 1997; Guo & Cooklock, 1996). The desirable attributes of an oral adhesive system for prolonged systemic delivery are a high drug loading capacity, good mucoadhesion, nonirritancy, good feel in the mouth, tastelessness, and sustained drug delivery. An erodible formulation has the added advantage of not requiring retrieval after delivery of the dose (Martin et al., 2003). In recent years, adhesive mucosal dosage forms were suggested for oral delivery, including adhesive solid drug delivery systems (tablets and patches) and adhesive semisolid drug delivery systems.

Adhesive Tablets

In order to improve the bioavailability of administrated drug in the oral cavity, several bioadhesive tablet systems have been developed in recent years (Beyssac et al., 1998; Bouckaert et al., 1993a). Adhesive buccal tablets can be applied to different sites in the oral cavity, i.e., the palate, mucosa of the cheek, and between the upper lip and gum. The tablet softens and adheres to the substrate and is retained in position until dissolution and/or release is complete. After a short time the presence of tablet is reported to be no longer noticeable to the patient. The tablet should not be moved about the mouth once in position, since this causes more rapid drug release. The position of successive tablets can be alternated on either side of the mouth. Patients wearing dentures may place the tablet in any comfortable position between the lip and gum (Chidambaram & Srivatsava, 1995).

The location of the tablet in the mouth appears to have a great impact on the tolerance and the retention time. Depending on the location, either palatal or gingival, retention times varied from 4–6 h to 7–12 h, respectively (Vivien-Castioni et al., 2000).

Usually, it is important that excipients of buccal tablets do not cause or stimulate salivation, since in this case a larger fraction of drug may be swallowed rather than becoming bioavailable or being absorbed.

Some systems have been developed and are already available on the market, such as Nicorette® (nicotine), Suscard® (glyceryl trinitrate), and Striant® (testosterone), while others are still in the development phase. The separate or associated polymers in these systems, as well as the drugs and processes used, are summarized in the Table 1.

At present, much effort is focused on the problems of absorption of high molecular weight compounds

TABLE 1 **Materials and Techniques Utilized to Prepare Buccal Bioadhesive Tablets**

Materials	Drug	Reference(s)
Thermally modified maize starch, carbopol 934, sodium benzoate, silicium dioxide[a]	Miconazole	Bouckaert et al., 1993a
Polyacrylic acid, thermally modified maize starch, sodium benzoate, silicium dioxide[a]	Miconazole	Bouckaert et al., 1993b
Drum-dried wax maize, carbopol 974P, sodium stearyl fumarate[a]	Testosterone	Voorspoels et al., 1996
Hydroxypropyl methylcellulose, stearic acid, silica gel, lactose anhydrous[a]	Glyceryl trinitrate	Walton & Rutland, 1998
Hydroxypropyl methylcellulose, carbopol 934, and magnesium stearate[a]	Fluoride	Garcia et al., 1998
2-hydroxymetacrylate, methylmetacrylate, and poly(methylmetacrylate)[b]	Fluoride	Lara et al., 1998
Polyoxyethylene, polyisobutylene, and polyethyleneglycol[a]	Vitamin B_{12}	Tiwari et al., 1999a
Carbopol 974P, hydroxypropyl methylcellulose, sodium lauryl sulphate, magnesium stearate[a]	Pentazocine	Agarwal & Mishra, 1999
Hakea gum[a]	Chlorpheniramine/calcitonine	Alur et al., 1999a, 1999b
Sodium alginate, hydroxypropyl methylcellulose, carbopol 934P, and polycarbophyl[a]	Omeprazole	Choi & Kim, 2000
Sodium alginate, hydroxypropyl methylcellulose, magnesium oxide and sodium croscarmellose[a]	Omeprazole	Choi et al., 2000
Pectin and hydroxypropyl methylcellulose[c]	Diltiazem	Miyazaki et al., 2000
β-cyclodextrin, Methocel, and polycarbophil[a]	Danazole	Jain et al., 2002
Carbopol 934P, Methocel, mannitol, and magnesium stearate[a]	Diltiazem hydrochloride	Singh & Ahuja, 2002
Hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, magnesium stearate, and mannitol[a]	Cetylpyridinium chloride	Ali et al., 2002
Hydroxypropylcellulose, carbopol 934, mannitol, lactose, polyvinylpyrolidone, and magnesium stearate[a]	Nicotine	Park & Munday, 2002
Starch-*g*-poly(acrylic acid) copolymers and starch/poly(acrylic acid) mixtures[a]	Testosterone	Ameye et al., 2002
Carbopol and hydroxypropylcellulose[a]	Ergotamine	Tsutsumi et al., 2002
Carboxymethyl cellulose, carbomer, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl methylcellulose, and acacia[a]	Nifedipine	Varshosaz & Dehghan, 2002
Polycarbophyl-cysteine conjugates[a]	Leu-enkephalin	Langoth et al., 2003

[a]Direct compression.
[b]Thermal molding.
[c]Molding.

such as peptide and proteins, mainly because their oral bioavailability is poor. Oxytocin, chymotrypsin, and insulin are some of the drugs administered by the buccal route (Langoth et al., 2003). However, a substantial sum of efforts is still necessary to improve the rate and extent of absorption of these molecules across the buccal mucosa. The utilization of permeability enhancers and their impact on the physiology of the oral cavity also need to be investigated.

It is important to point out the possible problems that children and elderly individuals may experience with the use of adhesive tablets. Among the potential problems is the possible discomfort provoked by the material applied to the mucosa and the possibility of the dosage form separating from the mucosa, being swallowed, and then adhering to the wall of the esophagus.

Adhesive Patches

Bioadhesive patches are systems that may range from simple erodible and nonerodible adhesive films to more sophisticated systems, which can be designed to provide either unidirectional or multidirectional release of the drug (DeGrande et al., 1996; Guo & Cremer, 1999; Peh & Wong, 1999). The oral cavity mucosa is an ideal surface for the placement of retentive delivery systems such as patches, since it contains a large expanse of smooth and immobile tissue (Harris & Robinson, 1992). Mucoadhesive patches for administration to the mucosa of the oral cavity may have a number of different designs, depending on various considerations, such as the therapeutic aim and the physicochemical and pharmacokinetic properties of the active ingredient. Regarding the therapeutic aim, two different rationales for developing mucosal patches may be considered: patches can be intended to deliver a drug to the systemic circulation in a way that is superior to other routes of administration, or their purpose may be local therapy of the oral mucosa. As alternatives for both classes of patches, more conventional dosage forms are available. In the case of locally acting patches, the alternatives most often used today are oral gels, oral liquids, and lozenges. For systemic action, there are a number of dosage forms, including sustained- or controlled-release oral technologies, transdermal patches, and injectable depot formulations. It is necessary for a successful mucosal patch to have clearly defined advantages over alternative products. Oral mucosal patches can be applied directly to the affected mucosal region and have the potential to supply the site of action with effective drug levels and to sustain these levels over a prolonged period of time. In contrast, conventional therapy exposes the affected tissues to the dose for a very short period of time (Guo & Cremer, 1999).

Thus, the first step in the development of a patch is the selection and characterization of a polymer with appropriate bioadhesive properties and drug release control or of combined polymers in order to obtain both of these properties (Guo, 1994; Li et al., 1998).

To the more sophisticated patches, which are usually composed by several materials, the formulation constituents are homogeneously mixed and compressed to a predetermined thickness, and appropriate sizes are cut or punched out. As with transdermal patch formulation, an impermeable backing layer should be considered for oral patches to prevent drug loss and for convenient application by the patient. Multilayer systems can be prepared by recompressing two superimposed patches. They can be spray-coated by air-spray units that can contain individual different backing materials (Guo & Cooklock, 1996). The main polymers and drugs used to prepare these kinds of patches are listed in Table 2.

A suitable oral bioadhesive drug delivery system should be flexible, elastic, soft, adequately strong to withstand breakage due to stress from mouth activities, and possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. Patches should be able to meet these requirements and swell to a certain extent when placed in aqueous medium (Peh & Wong, 1999; Wong et al., 1999b). They also ensure more accurate dosing of the drug compared to gels and ointments (Nafee et al., 2003).

The more sophisticated patches are not suitable for delivery of antimicrobial agents directly into the periodontal pocket. The use of nonbiodegradable polymers, the necessity of system removal at the end of therapy, the low flexibility and elasticity, potential immunological reactions, tissue sensitization, and difficult application to the periodontal pocket limit this application (Jones et al., 1996; Wong et al., 1999a). Thus, the use of polymeric films for oral mucosal drug delivery has been investigated (Kohda et al., 1997), although they have been more extensively

TABLE 2 Materials and Drugs Used to Prepare Oral Bioadhesive Patches

Materials	Drug	Reference
Polyurethane	Lignocaine	Brook et al., 1989
Hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol	–	Chidambaram & Srivatsava, 1995
Polyisobutylene, polyisoprene, Carbopol 974P	Buprenorphine	Guo, 1994
Silicone polymers	Peptides	Li et al., 1998
Hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, and Carbopol	Metoprolol tartrate	Wong et al., 1999b
Sodium carboxymethyl cellulose, chitosan, polyvinyl alcohol, hydroxyethyl cellulose, and hydroxypropyl methylcellulose	Miconazole nitrate	Nafee et al., 2003
Polycarbophil, Eudragit S-100, and pharmaceutical wax	Plasmid DNA (CMV-β-gal) or β-galactosidase protein	Cui & Mumper, 2002a
Polycarbophil, Eudragit S-100, and pharmaceutical wax	Synthetic salmon calcitonin	Cui & Mumper, 2002b

employed in pharmaceutical tablet coating formulations to improve appearance, to mask undesirable taste, and to control drug release (Peh & Wong, 1999). Oral bioadhesive films may be preferred over other patches or adhesive tablets in terms of flexibility, comfort, and easy application to the periodontal pocket. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva (Anders & Merkle, 1989; Collins & Deasy, 1990). Moreover, a polymeric adhesive film is able to protect the wound surface, thus reducing pain and treating the oral disease more effectively (Peh & Wong, 1999).

The major method of polymeric film manufacture is the solvent evaporation process, in which the polymeric material, with or without plasticizer, is dissolved in a solvent or solvent mixture and into which the active constituent is dissolved or dispersed. This solution is then cast onto a suitable substrate and the solvent is allowed to evaporate, leaving a solid polymeric film containing the drug (Jones & Medlicott, 1995). However, other techniques have also been used (Repka et al., 2004). Hot-melt extrusion technology has been proposed as a promising technique for films, resulting in shorter and more efficient processing times to a final product, environmental advantages due to elimination of solvents in processing, and increased efficiency of drug delivery to the patient (McGinity et al., 2001; Repka & McGinity, 2000a, 2000b, 2001a, 2001b; Repka et al., 1999). It was demonstrated that this technology is viable to prepare mucoadhesive matrix films intended for oral cavity clotrimazole delivery for the prophylaxis and treatment of oral candidiasis (Repka et al., 2003).

Besides the ideal characteristics for a suitable oral bioadhesive drug delivery system, an ideal oral film can present swelling. Film swelling, if present, should not be too extensive in order to prevent discomfort. Thus, the mechanical, bioadhesive, and swelling properties of film are critical and their evaluation is essential (Peh & Wong, 1999).

The suitability of films containing sodium carboxymethyl cellulose/polyethylene glycol 400/Carbopol 934P and hydroxypropyl methylcellulose/polyethylene glycol 400/Carbopol 934P was investigated. It was observed that the increase in Carbopol 934P content elevated the elasticity, softness, and bioadhesive strength, but decreased the strength and degree of swelling of both films. Correlation existed between the in vivo and in vitro bioadhesion data within the polymer, but no rank correlation was observed between the two polymers. Thus, films prepared with hydroxypropyl methylcellulose/polyethylene glycol 400/Carbopol 934P may be preferred over sodium carboxymethyl cellulose/polyethylene glycol 400/Carbopol 934P films as a drug vehicle for buccal delivery,

since the former were tougher, more elastic, more bioadhesive in vivo, and swelled in a more tolerable manner in the oral cavity than the latter (Peh & Wong, 1999).

Copolymers of acrylic acid and 2-ethylhexyl acrylate for buccal administration were designed, synthesized, and tested. It was observed that incorporation of 2-ethylhexyl acrylate improved the mucoadhesive performance of poly(acrylic acid). The copolymer consisting of a 1:1 mole ratio of the repeat units afforded the most favorable mucoadhesive profile. Of the two factors of contact time and cross-sectional area, the latter was found to have a more pronounced effect on mucoadhesive strength. In order to investigate the possibility of achieving buccal delivery of acyclovir, poly(acrylic acid) sodium salt (PAA) was used to prepare films with chitosan hydrochloride (HCS). The addition of PAA to HCS produced a reduction in the drug release profile. The film based on a 1/1.3 HCS/PAA weight ratio, besides possessing the best properties of resilience on the mucosa, was also characterized by the highest permeation profile and, therefore, represents a promising formulation for buccal delivery of acyclovir (Shojaei et al., 2000). Moreover, a gelatin film with strongly bioadhesive force was developed by introducing free dandling aldehyde groups from glutaraldehyde cross-linking (Matsuda et al., 1999).

Adhesive buccal films were developed in order to improve the drug bioavailability. Two dosage forms, a bioadhesive disc and a fast dissolving disc for buccal and sublingual administration of thiocolchicoside, respectively, were designed. The fast-dissolving (sublingual) form resulted in a quick uptake of 0.5 mg of thiocolchicoside within 15 min, whereas with the adhesive buccal form the same dose can be absorbed over an extended period of time (Artusi et al., 2003).

Attention has been focused on the local drug delivery system as a means to ensure the efficacy of locally administered antibiotics in periodontal therapy. This delivery system is produced by immobilizing antibiotic and antimicrobial agents with a carrier substance to provide controlled local release (Minabe et al., 1989). Cast films of ethylcellulose, with or without polyethylene glycol containing 5%, 10%, and 20% chlorhexidine diacetate, were developed for insertion into periodontal pockets for periodontal disease. The systems exhibited sustained release of the drug for several months (Friedman & Golomb, 1982). The release of chlorhexidine from ethylcellulose films cast from solvents of different dichloromethane/ethanol compositions was also studied (Jones & Medlicott, 1995). They observed that release rate was proportional to the square root of time. Increased ethanol content within the casting solvent significantly enhanced the rate of release. Release rate and cumulative mass released at different time intervals (5, 10, 15, and 25 days) were proportional to the solubility of the casting solvent. A degradable sustained-release device composed of a cross-linked protein containing chlorhexidine as the therapeutic agent was developed as a new dental drug delivery system to be used as an adjunct in the treatment of periodontal diseases (Steinberg et al., 1990). The results of the assessment of tetracycline systems immobilized on atelocollagen have suggested that, when topically administered, these systems remain both clinically and bacteriologically effective for 2 to 3 weeks (Minabe et al., 1989).

The use of buccal films for oral mucosal drug delivery of vaccines has been reported. The oral buccal mucosa may be an ideal site for mucosal immunization, allowing for the needle-free administration of cost-effective vaccines (Cui & Mumper, 2002a). Bilayer films were developed using polycarbophil and Eudragit S-100 as the mucoadhesive layer and a pharmaceutical wax as the impermeable backing layer. They were post-loaded with plasmid DNA (CMV-β-gal) or β-galactosidase protein. The weight ratio of polycarbophil and Eudragit S-100 had a significant effect on adhesion time of films. Post-loaded plasmid DNA and β-galactosidase protein remained stable after released from films. The feasibility of buccal (genetic) immunization with these novel bilayer films was demonstrated. These same mucoadhesive bilayer films were also used as an alternative and more cost-effective dosage form for delivery of calcitonin, resulting in the delivery of therapeutically efficacious amounts of calcitonin across the buccal mucosa in rabbits (Cui & Mumper, 2002b).

Today, buccal patches intended to deliver drug systemically have clearly received more attention from the scientific community than the patches used for local delivery of drug. Thus, bioadhesive patch formulations are certainly promising alternatives for drug delivery systems (Guo & Cremer, 1999; Nafee et al., 2003).

Adhesive Semi-solid Systems

Adhesive semi-solid systems based on hydrogels are an attractive dosage form. They may be used to deliver the drug via buccal mucosa or intra-periodontal pocket with the possibility of prolonging residence time and improving bioavailability (Chidambaram & Srivatsava, 1995; Jones et al., 1996). Hydrogels are formed from polymers and may be hydrated in an aqueous environment without dissolution, acting as drug delivery systems by physically entrapping molecules, which are then slowly released by diffusion or erosion after gel hydration (Martin et al., 2003). Semi-solid systems have the advantage of being deliverable with a syringe, with a consequent easy placement in periodontal pockets (Needleman, 1991) and easy dispersion throughout the mucosa of oral cavity.

The main drawback of many drug delivery systems, especially semi-solid ones designed for use in the oral cavity, is poor retention at the site of application when the hydrogel polymer has no adhesive properties. This drawback may be minimized or eliminated by the incorporation of a bioadhesive polymer into the formulation (Jones et al., 1996). Moreover, the formulation retention time at the site of application is related to bioadhesive efficacy, and the rate and extent of release depend on the physico-chemical characteristics of the drug and the dosage form. Thus, the release properties can be controlled by qualitative and/or quantitative manipulation of the drug components.

There is a variety of materials that have been used in semi-solid drug delivery systems development. Systems based on hydroxyethyl cellulose, polyvinylpyrrolidone and polycarbophil (as an adhesive polymer), and tetracycline (model drug), have been produced with various proportions of hydroxyethyl cellulose and polyvinylpyrrolidone, according to a factorial design. Increased concentrations of hydroxyethyl cellulose decreased the rate of release of tetracycline due to the increased viscosity and the decreased rate of diffusion. Conversely, an increased polyvinylpyrrolidone concentration increased tetracycline release rates due to an increased formulation porosity following dissolution of this polymer. Increased concentrations of hydroxyethyl cellulose and polyvinylpyrrolidone increased the hardness (force required to attain a given deformation), compressibility, and syringeability due to increased product viscosity and to parameters related to bioadhesion, illustrating the adhesive nature of polymers, and enhanced the semi-solid nature of the product, resulting in decreased product elasticity and cohesiveness. The interactions between the polymers were statistically significant when observed within the factorial design with respect to rate of release and all mechanical properties. These interactions arose because of variations in the physical states (dissolved or dispersed) of polymeric formulation components. All formulations demonstrated slow release and zero order kinetics for a period between 24 and 54 hours, with specific release between 1.59 and 15.80 mg/h (Jones et al., 1996). Similar formulations containing flubiprofen or tetracycline hydrochloride were studied in humans and demonstrated good clinical efficacy (Jones et al., 1999, 2000).

Also, for the treatment of periodontal diseases, the effect of subgingival irrigation with a 1% chlorhexidine collagen gel in periodontal pockets as an adjuvant procedure to scaling and root planing has been evaluated. It was concluded that 1% chlorhexidine collagen gel is a promising adjuvant to scaling and root planning in the treatment of adult periodontitis. There was an improvement in clinical parameters in all tested groups with a significantly greater decrease in gingival recession and bleeding in the chlorhexidine group (Vinholis et al., 2001).

Moreover, in dentistry and oral medicine, there are various applications of chitosan, an agent with bioadhesive, biocompatibility, biodegradability, and antimicrobial properties. The release of drugs from chitosan may be modulated by its exclusive use or by its use in combination with polymers of different molecular weight and with different degrees of acetylation. Formulations (gel and film) containing chitosan (1.0% or 2.0%) and chlorhexidine (0.1% or 0.2%) were prepared and their properties were studied. The flow property of the gels was found to be suitable for topical application to the oral mucosa and for injection into the periodontal pocket with a syringe. Both the film and gel formulations exert bioadhesive properties and are not affected by incorporation of chlorhexidine. In vitro release of chlorhexidine from gels and films were maintained for 3 hours and no lag-time in release was observed. The highest antifungal activity was obtained with 2% chitosan, gel and film

form, against the periodontal pathogen *Porphyromonas gingivalis*. The combination of chitosan with chlorhexidine showed a higher activity when compared to that of chlorhexidine alone. This would permit the application of chlorhexidine at lower concentrations, thus preventing its unwanted side effects. Chitosan films and gels, with their bioadhesive property and antimicrobial activity, seem to be promising delivery systems for the local treatment of periodontal diseases (Ikinci et al., 2002).

In animal models, bioadhesive gels have been shown to enhance the bioavailability of drugs by buccal administration. The bioavailability of drugs by buccal administration can be improved by the incorporation of permeability enhancers into the formulation. It was demonstrated in animals (rabbits) that gels containing sodium deoxycholate increase by 1.59 times the relative bioavailability of the triamcinolone acetonide (2.0 mg), similar to the absolute bioavailability of 1 mg (intravenous administration), showing relatively constant sustained blood concentration with minimal fluctuations (Shin et al., 2000). Chitosan gel bases have been investigated in order to transmit and to increase the penetration of large molecules, especially bioactive peptides. Chitosan gel was found to exert the marked permeabilizing effect on growth factor-b (TGF-b) in porcine oral mucosa when appraised by horizontal sectioning localization.

The delivery of hydrophobic drugs is usually obtained using hydrogels from polymer mixtures. Martin et al. (2003) evaluated a physically cross-linked palmitoyl glycol chitosan hydrogel, with different hydrophobicities, in a controlled-release system for the delivery of denbufylline, with and without glycodeoxycholate as a permeability enhancer. Denbufylline reduced the porosity, erosion, and hydration of the gels while glycodeoxycholate increased the hydration and erosion.

EVALUATION STRATEGIES

Satisfactory bioadhesion is essential for the successful application of a bioadhesive drug delivery system in the oral cavity. The main feature of bioadhesion is the strength of attachment of the dosage form to the biological tissue (Wong et al., 1999b). Several test methods have been reported in the literature for studying buccal bioadhesion (Bouckaert et al., 1993a). These tests are necessary to screen a large number of candidate mucoadhesives and to study their mechanisms. These tests are also important during the design and development of a controlled-release oral bioadhesive system, since they ensure compatibility, physical and mechanical stability, surface analysis, and bioadhesive bond strength. A good review about the methods used to study bioadhesion was presented by Ahuja et al. (1997), who classified the test methods into two major categories, i.e., in vitro/ex vivo methods and in vivo methods.

The in vitro/ex vivo methods based on measurement of tensile strength (force required to break the adhesive bond between a model membrane and the test polymers) use a model membrane (substrate) that is a tissue-model obtained from gastrointestinal mucosa (esophagus, stomach, intestine, etc.), sublingual mucosa, buccal mucosa, gingival, or peritoneal membranes of animals (mouse, pig, rabbit, bullock, rats, hamster, or guinea pig). If the duration of bonding of the bioadhesive system to substrate is to be investigated over significantly long periods, then attempts must be made to maintain the morphology and integrity of the tissue-model. Deterioration of the mucosa could result in adhesive behavior different from the in vivo application. Organ culture techniques allow complete tissues to be maintained for long periods of time and might provide a suitable means for the study of duration (Needleman & Smales, 1995). The results of the studies provided important information regarding the effects of charge density, hydrophobicity, and experimental conditions such as pH, ionic strength, mucolytic agents, and applied pressure on bioadhesion. The instruments usually employed to measure tensile strength are modified scales, tensiometers, or tensile testers. In the last 5 years, these methods have been extensively used and refined (Table 3).

Another in vitro/ex vivo method described is based on measurement of shear strength (Ahuja et al., 1997). Shear stress measures the force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. The method uses a glass plate suspended from a microbalance that is dipped in a temperature-controlled mucus sample. The force required to pull the plate out of the solution is determined under constant experimental conditions. Over the last few years, the bioadhesion of

TABLE 3 The Newest Bioadhesion Measurements in Tensile Strength Investigations

Bioadhesive	Substrate	Instrument	Reference(s)
Silicone polymers, CP 974P	Rabbit buccal mucosa	Tensile apparatus (Instron, U. K.)	Li et al., 1998
Hakea gum, bicarbonate, tartaric acid	Rabbit intestinal mucosa	LTC universal tension-compression stand equipped with model DFM-10 digital force gauge (Chatillon, NC)	Alur et al., 1999a, 1999b
P(AA-co-EHA)	Porcine buccal mucosa	Tensile apparatus (Instron, Canton, MA, USA)	Shojaei et al., 2000
Sodium alginate, HPMC	Hamster cheek pouch	Modified balance	Choi & Kim, 2000
Polycarbophil, HPMC	Cellulose acetate membrane impregnated with porcine mucin solution (5%)	Tensile tester (Chatillon, Greensboro, NC)	Jain et al., 2002
CPC, NaCMC, HPMC	Bovine cheek pouch	Modified pan balance	Ali et al., 2002
CP 934P, HPMC	Porcine buccal mucosa	Modified pan balance	Singh & Ahuja, 2002
CMC, CP, PVP, PVA, HPMC, acacia	1% mucus sample or sodium alginate gel	Modified tensiometer	Varshosaz & Dehghan, 2002
Polycarbophil-cysteine conjugate	Porcine intestinal mucosa	Modified balance	Langoth et al., 2003

Note: CP = Carbopol; CPC = Cetylpyridinium chloride; HPMC = Hydroxypropyl methylcellulose; P(AA-co-EHA) copolymers of acrylic acid and 2-ethylhexyl acrylate; PVA = Polyvinyl alcohol; PVP = Polyvinylpyrrolidone; NaCMC = Sodium carboxymethyl cellulose.

gelatin films cross-linked with glutaraldehyde has been evaluated using two porcine skins. Bonding strength was measured by shear strength using a tensile instrument (Autograph; Shimadzu Inc., Kyoto, Japan) (Matsuda et al., 1999).

Today, the tensile test using a texture profile analyzer (TPA) is a useful technique that has been extensively employed as a valid means for mechanical characterization of pharmaceutical buccal bioadhesive solid and semi-solid dosage forms (Eouani et al., 2001). The physical properties of the bioadhesive formulations can be examined using TPA to determine the following parameters (Jones et al., 1996): product hardness (force required to attain a given deformation); adhesiveness (the work necessary to overcome the attractive forces between the surface of the sample

TABLE 4 Bioadhesion Measurements by TA-XT2 Texture Analyzer Equipment

Bioadhesive	Dosage form	Reference(s)
HEC, PVP, PC	Gel	Jones et al., 1996
HEC, SCMC	Gel	Jones et al., 1997
HEC, PVP, PC	Gel	Jones et al., 1999
Eudragit, HPMC, SCMC, CP, PC, PVP, alginic acid, gelatin, chitosan	Patch	Wong et al., 1999a, 1999b
SCMC, PEG, CP 934P	Film	Peh & Wong, 1999
HEC, PVP, PC	Gel	Jones et al., 2000
PVP, CP 971P, PC, SCMC, carrageenan	Film	Eouani et al., 2001
PVP, CP 934, HPC	Tablet	Park & Munday, 2002
Chitosan	Gel and film	Ikinci et al., 2002
PGC	Gel and tablet	Martin et al., 2003

Note: CP = Carbopol; HEC = Hydroxyethyl cellulose; HPC = Hydroxypropyl cellulose; HPMC = Hydroxypropyl methylcellulose; PC = Polycarbophil; PEG = Polyethylene glycol; PVP = Polyvinylpyrrolidone; SCMC = Sodium carboxymethyl cellulose; PGC = Palmitoyl glycol chitosan.

and the surface of the probe); compressibility (the work required to deform the product during the first compression of the probe); elasticity (the ratio of the time required to achieve maximum structural deformation on the second compression cycle to that on the first compression cycle, where successive compressions are separated by a defined recovery period); cohesiveness (the ratio of the area under the force-time curve produced in the second compression cycle to that produced on the first compression cycle, where successive compressions are separated by a defined recovery period).

Most investigations describe the use of the Stable Micro Systems TA-XT2 texture analyzer (Haslemere, Surrey, U.K.). Many reports describe the use of this equipment to evaluate oral adhesive tablets, gels, ointments, patches, and films (Table 4).

Using a fluorescent probe method, an ex vivo system based on porcine buccal membranes was developed to demonstrate the bioadhesive effects of polysaccharides and polysaccharide-containing herbs on buccal membranes (Schmidgall et al., 2000). The test system was shown to discriminate the adhesive effects of different raw polysaccharides obtained from a variety of medicinal plants.

Atomic force microscopy (AFM) has also been used for oral bioadhesive systems (Patel et al., 2000). Standardized buccal cells were added to polymer solutions and bioadhesion was evaluated, showing that AFM is a sensitive technique for imaging the presence of adsorbed bioadhesive polymers on mucosal cell surfaces under the conditions of minimal sample preparation. The imaging methods described are relatively simple, in that they make use of contact mode, topographic operation, and as such, they are only able to provide qualitative and semi-quantitative information regarding cell coverage. Changes in surface topography were indicative of the presence of bound polymer. This is an experimental method that provides strong additional supporting evidence about bioadhesion.

A direct method to evaluate the mucoadhesion of polymers from an aqueous dispersion, both in vitro and in vivo, was also described (Kockisch et al., 2001). Adhering polymer was visualized by staining with either 0.1% (w/v) Alcian blue or eosin solution. The extent of polymer adhesion was quantified by measuring the relative staining intensity of control and polymer-treated cells by image analysis.

Most of the in vivo studies of the buccal adhesive drug delivery systems described in the literature focus on the assessment of the bioavailability of the drug contained in them (Cui & Mumper, 2002b; Eouani et al., 2001; Ikinci et al., 2002; Jones et al., 1999; Martin et al., 2003; Needleman, 1991; Shin et al., 2000; Varshosaz & Dehghan, 2002; Vinholis et al., 2001). In vivo techniques for measuring bioadhesive strength are relatively few, especially for oral bioadhesive systems. Some of the reported methods are based on the measurement of the residence time of oral bioadhesives at the application site (Ahuja et al., 1997).

It is very important to study the bioadhesion by both in vitro/ex vivo and in vivo methods and to determine the correlation between them. An in vitro/in vivo correlation study on the bioadhesive properties of three buccal formulations based on modified starch/polyacrylic acid mixture was performed (Bouckaert et al., 1993b). The in vitro method showed no significant influence of miconazole nitrate on the bioadhesion properties of the polymers, while the in vivo adhesion time of the pure polymer mixtures was significantly longer than for the polymers containing miconazole. The addition of 10% miconazole to the tablet formulation must have induced a decreased resistance to erosion in comparison to the tablet made of pure polymers. Therefore, the results

TABLE 5 **In Vivo Methods Used to Study Bioadhesion**

Method description	Subject	Reference (s)
Clinical evaluation	Human volunteers	Jones et al., 1999
Placebo buccal bioadhesive device	Adult male beagle dogs	Tiwari et al., 1999a, 1999b
Residence time investigation	Human volunteers	Peh & Wong, 1999
Clinical evaluation	Human volunteers	Jones et al., 2000
Bioadhesive force evaluation	Human volunteers	Choi & Kim, 2000
Evaluation of buccoadhesive erodible disk	Human volunteers	Ali et al., 2002
Study of the drug release	Human volunteers	Nafee et al., 2003

obtained with the in vitro method did not correlate well with the in vivo data and an in vitro method for the assessment of erosion may be necessary for optimization of a buccal bioadhesive dosage form. The in vitro method provided information only on the initial bioadhesion and no correlation could be established with the residence time of the tablet in the oral cavity. Some investigations using in vivo methods to study bioadhesion were first described by Ahuja et al. (1997), with many others having been developed since (Table 5).

MATERIALS

Bioadhesive materials that can adhere to soft tissues have great potential for medical applications (Matsuda et al., 1999). Polymers that can form adhesive interactions with biological substrates have been reported by several authors to offer certain advantages for drug delivery, including prolonged residence time and improved location on specific sites (Jones et al., 1997).

A wide range of polymers, both natural and synthetic, have been studied for their potential use as mucoadhesives. The polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad categories: 1) polymers that become sticky when placed in water and owe their bioadhesion to stickiness; 2) polymers that adhere through nonspecific, noncovalent interactions that are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant); 3) polymers that bind to specific receptor sites on the cell surface (Glantz et al., 1999; Huang et al., 2000; Peppas & Sahlin, 1996).

Polymers that can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. Among these "superglues," polymers and monomeric alpha-cyanoacrylate esters have been most frequently investigated and used. Other synthetic

TABLE 6 Oral Bioadhesive Polymers (Alone or in Combination)

Polymer	Reference(s)
Poly(acrylic acid), modified maize starch[a]	Bouckaert & Remon, 1993
Polyoxyethylene, polyethylene glycol[a]	Tiwari et al., 1999b
Carbopol, hydroxypropyl methylcellulose, gelatin[a]	Vivien-Castioni et al., 2000
Carbopol 934P, ethylcellulose, polyvinylpyrrolidone, cellulose acetate, poly(ethylene-co-vinyl acetate)[b]	Guo & Cooklock, 1996
Chitosan, poly(ethylene oxide), sodium carboxymethyl cellulose, xanthan gum, poly(acrylic acid), Carbopol, polycarbophil[d]	Needleman & Smales, 1995
Hydroxyethyl cellulose, sodium carboxymethyl cellulose[d]	Jones et al., 1997
Hydroxyethyl cellulose, polyvinylpyrrolidone, polycarbophil[d]	Jones et al., 1996, 1999, 2000
Poloxamer 407, Carbopol 934[d]	Shin et al., 2000
Chitosan[d]	Ikinci et al., 2002; Senel et al., 2000
Collagen[d]	Vinholis et al., 2001
Palmitoyl glycol chitosan[d]	Martin et al., 2003
Ethylcellulose[c]	Friedman & Golomb, 1982
Atelocollagen[c]	Minabe et al., 1989
Cross-linked protein[c]	Steinberg et al., 1990
Ethylcellulose[c]	Jones & Medlicott, 1995
Hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, poly(acrylic acid), Carbopol 934P, polyethylene glycol 400[c]	Peh & Wong, 1999
Gelatin[c]	Matsuda et al., 1999
Poly(acrylic acid-co-ethylhexyl acrylate)[c]	Shojaei et al., 2000
Chitosan[c]	Senel et al., 2000
Chitosan hydrochloride, poly(acrylic acid)[c]	Rossi et al., 2003
Gelatin, carboxymethyl cellulose[c]	Artusi et al., 2003

[a]Tablet.
[b]Patch.
[c]Film.
[d]Semi-solid.

polymers such as polyurethanes, epoxy resins, polystyrene, acrylates, and cements from natural products, and glues have also been extensively investigated. Cationic and anionic polymers bind more effectively than neutral polymers; polyanions are better than polycations in terms of binding/potential toxicity; water-insoluble polymers provide greater flexibility in dosage form design compared to rapidly or slowly dissolving water-soluble polymers; anionic polymers with sulphate groups bind more effectively than those with carboxylic groups; degree of binding is proportional to the charge density on the polymer (Park & Robinson, 1984).

An ideal polymer for an oral bioadhesive drug delivery system should have the following characteristics (Ahuja et al., 1997; Guo & Cooklock, 1996; Peh & Wong, 1999):

1. The polymer and its degradation products should be nontoxic and not absorbed through the mucous membrane.
2. It should not irritate the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to moist tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose during storage or during the shelf-life of the dosage form.
7. The cost of the polymer should not be high, so that the prepared dosage form remains competitive.
8. The polymer should allow flexibility and comfort of the dosage form.

Moreover, some of mucoadhesive polymers were found to inhibit proteolytic enzymes and/or modulate the permeability of tight epithelial tissue barriers (Lehr, 1996). Such features were found to be useful in the context of peptide and protein drug delivery, especially in the oral mucosa (Zhang & Robinson, 1996). Oral bioadhesive polymers currently utilized are presented in Tables 1, 2, and 6.

CONCLUSIONS

The oral mucosa possesses a range of permeabilities and properties. The smooth and relatively immobile surface of the oral cavity is suitable for placement of a bioadhesive dosage form for sustained delivery of therapeutic agents.

Oral bioadhesive dosage forms have many advantages over traditional oral dosage forms. Adhesive tablets, unlike conventional tablets, allow drinking and speaking without major discomfort. Adhesive semi-solids may be used to deliver the drug via the oral mucosa with the possibility of prolonging residence time and improving bioavailability. Moreover, an adhesive semi-solid may be easily applied to the periodontal pocket using a periodontal syringe, being retained within the pocket for long periods of time. Adhesive patches may range from simple erodible and nonerodible adhesive films to sophisticated systems and can be designed to provide either unidirectional or multidirectional release of the drug. Oral bioadhesive polymeric films may be preferred in terms of flexibility, comfort, and easy application to the periodontal pocket. In addition, they can circumvent the relative short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. The choice of better oral bioadhesive dosage forms also depends on the characteristics of the drugs and on the site to be treated (periodontal pocket, gingiva, teeth, cheek mucosa, or systemic).

Drugs with short biological half-lives, requiring a sustained effect and/or exhibiting sensitivity to enzymatic degradation in the intestinal tract, may be successfully delivered via oral bioadhesive delivery systems.

Today, research on oral bioadhesive drug delivery systems continues at a rapid pace, aiming at successful treatment of common oral lesions (aphthae, ulcerations, etc.), periodontitis, gingivitis, and dental caries. Optimizing systemic treatment of disease via transmucosal drug delivery from the oral cavity continues to be investigated using a variety of dosage forms containing novel bioadhesive polymers.

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