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Buccal drug delivery

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Buccal formulations have been developed to allow prolonged localised therapy and enhanced systemic delivery. The buccal mucosa, however, while avoiding first-pass effects, is a formidable barrier to drug absorption, especially for biopharmaceutical products (proteins and oligonucleotides) arising from the recent advances in genomics and proteomics. The buccal route is typically used for extended drug delivery, so formulations that can be attached to the buccal mucosa are favoured. The bioadhesive polymers used in buccal drug delivery to retain a formulation are typically hydrophilic macromolecules containing numerous hydrogen bonding groups. Newer second-generation bioadhesives have been developed and these include modified or new polymers that allow enhanced adhesion and/or drug delivery, in addition to site-specific ligands such as lectins. Over the last 20 years a wide range of formulations has been developed for buccal drug delivery (tablet, patch, liquids and semisolids) but comparatively few have found their way onto the market. Currently, this route is restricted to the delivery of a limited number of small lipophilic molecules that readily cross the buccal mucosa. However, this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome. In particular, patient acceptability and the successful systemic delivery of large molecules (proteins, oligonucleotides and polysaccharides) via this route remains both a significant opportunity and challenge, and new/improved technologies may be required to address these.

Keywords: absorption, bioadhesion, buccal, buccoadhesion, mucoadhesion

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1. Introduction

The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gingivae (gums) and cheek (sometimes referred to as the buccal pouch) to treat local and systemic conditions. This review will confine itself to this description of buccal drug delivery, although in some texts the whole interior of the mouth is referred to as the buccal cavity.

One of the major issues for drug delivery scientists is the delivery of the new products generated by the genomics and proteomic revolution [1-4]. The pharmaceutical sciences now have to consider new strategies to effectively deliver the new biopharmaceutical products (typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides), as well as conventional small drug molecules, and the buccal route provides one potential route for achieving this.

The oral cavity has been used as a site for local and systemic drug delivery. Local therapy is used to treat conditions such as gingivitis, oral candidosis, oral lesions, dental caries and xerostoma, whereas systemic delivery carries the drug into the main circulation avoiding hepatic first-pass metabolism effects, in addition to the pH and digestive enzymes of the middle gastrointestinal tract. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued. Delivery systems used include mouthwashes, aerosol sprays, chewing gums, bioadhesive tablets, gels and patches [5]. The

challenges facing buccal drug delivery are typically related to whether local or systemic action is required [6-9]. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing. The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system [10-12] could mean that some areas of the oral cavity may not receive effective levels. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

This review will consider buccal drug delivery, the challenges, especially for the new biopharmaceutical products, and systems devised to address these, in addition to some recent studies in this area.

1.1 Anatomy and physiology

The anatomy and physiology of the oral cavity has been reviewed in many texts [7-9,13-15] and will be described briefly below. The interior of the mouth is divided into two regions, the outer and interior oral vestibules. The buccal pouch (outer oral vestibule) is the space between the cheeks or lips and the teeth, whereas the oral cavity proper (interior oral vestibule) is situated behind the teeth.

The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa (**Figure 1**). It also contains many sensory receptors including the taste receptors of the tongue. The buccal mucosa (on the inside of the cheek) consists of lining (non-keratinised) mucosa, whereas masticatory (keratinised) mucosa is found on the gingiva. The thickness of the mucosae varies from 500 to 800 mm for the buccal mucosa (40 – 50 cell layers) to 100 – 200 μm for the gingival mucosa [15]. The turnover time for cells in the buccal mucosa has been reported to be 3 – 8 days [15] and 14 – 24 days [16].

It is worth noting that the models for buccal epithelia used in many experiments, the rat oral cavity and hamster cheek pouch, are actually keratinised, so differ significantly from human buccal mucosa.

There are three major salivary glands (the parotid, submaxillary and sublingual) that secrete saliva into the oral cavity. Minor salivary or buccal glands are situated in or immediately below the mucosa. The parotid and submaxillary glands produce a watery secretion, whereas the sublingual glands produces mainly viscous (mucin containing) saliva with limited enzymatic activity. Saliva has the function of lubricating the oral structures, facilitating the oral phase of swallowing by enhancing the formation of a slippery food bolus, preventing demineralisation of the teeth, allows carbohydrate digestion (via amylases), regulating the oral microbial flora maintenaning the oral pH and soft tissue repair [17,18]. Saliva is a weak buffer and has a pH typically around neutral but varies depending on whether saliva secretion is stimulated (in anticipation of food) or background. The pH can also be reduced locally by the activity of certain caries-forming bacteria.

A salivary film (pellicle) is distributed over all the surfaces of the mouth, coating epithelial cells and dental enamel [19]. The thickness of the salivary film is calculated to be only 70 – 100 μm [20], although its thickness and properties will vary in different areas of the mouth, depending on the proximity to the ducts of the major and minor salivary glands. A human typically produces ~ 1 l/day of saliva; the resting flow is 0.5 ml/min, which can be increased to > 7 ml/min following maximal stimulation of the parasympathetic system (e.g., in anticipation of food) [15,17]. The parotid salivary gland makes up the majority of the stimulated saliva flow and this is secreted on either side of the upper buccal pouch above the second molar tooth.

The oral cavity contains a diversity of microorganisms; > 300 different species of bacteria have been isolated and identified. The density of microorganisms in the oral fluids is high; saliva, which derives its flora from oral surfaces, contains 10^7 – 10^8 bacteria/ml [21]. These bacteria rapidly form a biofilm (dental plaque) on top of and within the salivary pellicle on all surfaces within the oral cavity.

The process of eating, with the ingestion of fluids and solids and mouth movement during mastication and swallowing, also provides a significant challenge for a delivery system located in this region.

1.2 Permeability of oral mucosa

Drugs administered via the oral cavity are absorbed into the reticulated and jugular veins and then drained into the systemic circulation, avoiding hepatic first-pass elimination of the drugs. The superficial layers (approximately the outermost quarter) of the oral mucosa represent the primary barrier to the entry of substances from the exterior (although the lower layers have also been proposed to provide a significant barrier [22,23]). There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa: transcellular (intracellular, passing through the cell) and paracellular (intercellular, passing around the cell). Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules [16,24,25]. It has been argued, however, that the route taken depends on the physicochemical properties of the drug [26,27].

Generally, small molecules that are predominantly lipophilic, with a log P of 1.6 – 3.3, are absorbed most rapidly; above this value their limited water solubility restricts their absorption [28]. Most drugs delivered successfully via the buccal or sublingual route are, therefore, small and lipophilic, whereas large hydrophilic molecules are generally poorly absorbed. Thus, the salivary pH will have a pronounced effect on molecular charge, the relative hydrophilic/lipophilic nature of the drug, and its absorption from this route. It has been proposed that in the non-keratinised buccal and sublingual mucosae, the hydrophilic nature of the lipids means that this

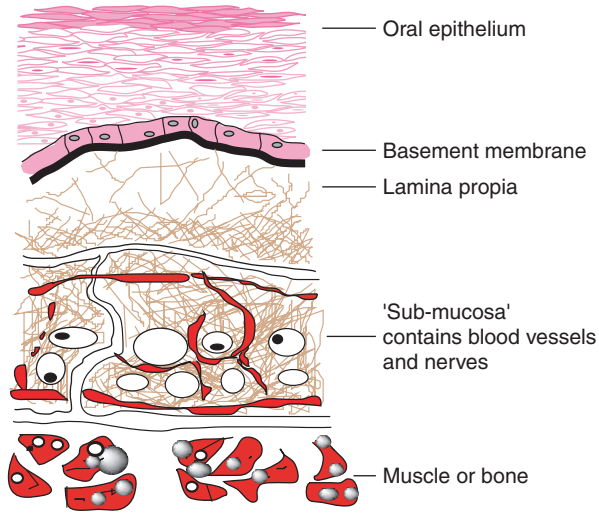


Figure 1. Cross-section through the oral mucosa.

is the predominant route for the absorption of hydrophilic molecules, whereas lipophilic molecules pass through the cell membranes and are absorbed by the transcellular route [26,27]. The amphiphilic nature of the intercellular lipids suggests that both a hydrophobic and hydrophilic pathway through the paracellular route are likely to exist [22]; the situation may, therefore, be more complex than the relatively simple models sometimes described. Although passive diffusion is the main mechanism of drug absorption [26,27], specialised transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients [29,30]; glucose and cefadroxil were shown to be absorbed in this way. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability [31], and absorption enhancers may be required to overcome this [32]. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability.

Disease states in which the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions.

1.3 Absorption enhancers

In order to overcome the barrier provided by the oral mucosae, especially for large molecules, absorption (permeation) enhancers have been included in formulations for buccal application. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin [32]. The penetration of some proteins was typically 1 – 3% *in vitro*, which on addition of an appropriate absorption enhancer, increased to 10% [22].

The most common absorption enhancers are fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Oleic acid has been reported to be a good absorption enhancer for insulin [33]. The fatty acids in cod liver oil have also been reported to enhance the buccal delivery of ergotamine [34]. Bile salts have been used extensively as penetration enhancers, and are believed to act by the extraction of lipids or proteins from the cell wall, membrane fluidisation and reverse membrane micellation without causing major damage to the buccal mucosa. Sodium dodecyl sulfate is reported to have a significant absorption-enhancing effect but may also damage the mucosa [22].

A range of other materials has also been reported to have absorption-enhancing effects. Solutions/gels of chitosan were found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium [35], chitosan glutamate being particularly effective. Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism [36].

Nicolazzo and colleagues [37] considered the use of the lipophilic skin-penetration enhancers octisalate, padimate (both used in sun screens) and laurocapram on the buccal absorption of various drugs *in vitro*. The former two had limited effect (although some increase in tissue uptake was proposed in some cases) whereas laurocapram was seen to enhance the permeation of triamcinolone acetonide, while reducing the penetration of oestradiol and caffeine.

The inhibition of enzymes that may degrade biopharmaceutical drugs can also enhance absorption and materials such as aprotinin [38] and puromycin [39] have been added to reduce peptide degredation.

2. Types of delivery systems for buccal drug delivery

Although a range of formulations are available for application within the oral cavity, generally the buccal cavity is used as a site for prolonged drug delivery (the sublingual region being favoured for rapid drug absorption). There are some non-attached formulations for buccal drug delivery (e.g., [40]). Commercial examples include Actiq® (Cephalon, Inc.), which is a 'lozenge on a stick' containing the analgesic fentanyl that is rubbed along the inside of the cheek, or OraVescent® (CIMA Laboratories) an effervescent tablet that rapidly releases fentanyl into the buccal pouch. However, most formulations require retention for extended periods, hence the development of bioadhesive systems.

2.1 Principles of bioadhesion

Bioadhesive formulations typically contain an adhesive material into which the drug is incorporated. The range of bioadhesives available for medical applications have been reviewed elsewhere [41]. The most widely investigated group of bioadhesives used in

buccal delivery systems are hydrophilic macromolecules containing numerous hydrogen bond-forming groups [9,42,43]; the so-called first-generation mucoadhesives. The mechanism of action of these materials has recently been reviewed [44], and is discussed briefly below. The presence of hydroxyl, carboxyl or amine groups on the molecules favours adhesion. They are called 'wet' adhesives as they are activated by moistening and will adhere nonspecifically to many surfaces. Unless water uptake is restricted, they may over hydrate to form a slippery mucilage. Typical examples are the polyacrylic acids (e.g., carbomer) and the polysaccharides such as chitosan and the cellulose derivatives (**Figure 2**). These were used initially as they were available 'off the shelf' with regulatory approval, but in the last few years, new enhanced materials have been developed with more favourable properties.

For dry or partially hydrated dosage forms two basic steps in mucoadhesion have been identified [44]. Step one is the 'contact stage' where intimate contact is formed between the mucoadhesive and mucous membrane. Within the buccal cavity the formulation can usually be readily placed into contact with the required mucosa and held in place to allow adhesion to occur. Step two is the 'consolidation' stage where various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion. Mucus gel dehydration by the bioadhesive polymer, and macromolecular interpenetration, have both been proposed as ways that strengthening of the mucus layer can occur [44,45]. Adhesive joint failure will normally occur within the weakest region of the bioadhesive joint. For weak adhesives this would be the adhesive interface, for weakly gelling materials this would be the hydrating layer, and for stronger adhesives this would initially be the mucus layer but later the hydrating adhesive material. The strength of the adhesive joint will, therefore, depend on the cohesive nature of the weakest region. In the buccal cavity, however, the thin salivary pellicle would rapidly dehydrate and collapse when placed in contact with a dry hydrophilic bioadhesive polymer, so adhesive failure within the mucus layer would be unlikely.

In order to strengthen the adhesive bond, thiol groups (by coupling cysteine, thioglycolic acid and cysteamine) have been placed into a range of mucoadhesive polymers such as the carbomers, chitosans and alginates by Bernkop-Schnuerch and colleagues [46-51]. *In situ* they form disulfide links between the polymers themselves but also with the mucin layer/mucosa itself [52].

Glyceryl monooleate/water (8 – 20%) liquid crystalline phases have also been used as bioadhesives in the buccal cavity. They differ significantly from the hydrophilic macromolecules used in most bioadhesive studies [53]. Mucoadhesion is said to occur after the uptake of water, allowing dehydration of the substrate, and an inverse relationship between water content and mucoadhesion was obtained.

Liquid and semisolid bioadhesion is typically a viscous liquid or gel clinging to, and being retained on, a mucous membrane, and is influenced by the thermodynamic affinity of the semisolid for the mucous membrane, the rheological properties and the formulation stability within the biological system [44]. It could be argued that it would perhaps be better to describe these formulations as 'retentive' rather than 'bioadhesive', as the process of bioadhesive bond formation described above may not take place. Adsorption of dissolved polymers onto a mucosal surface is also sometimes referred to as a type of bioadhesion.

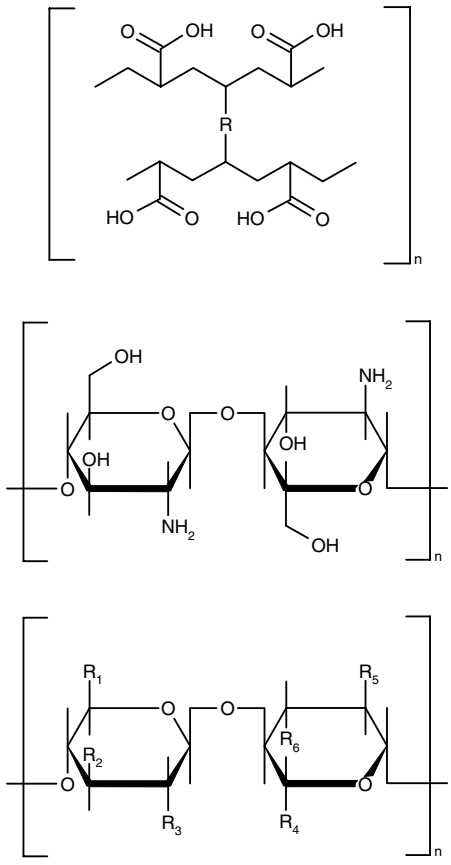
The stresses experienced by a formulation within the oral cavity will vary from region to region, with the gingival region, near the teeth, being subject to significant shearing stress during mastication and the upper buccal pouch, away from the openings to the salivary ducts, experiencing relatively minor dislodging stresses. Salivary and ingested liquid pooling would occur in the lower buccal pouch whereas mucin is secreted by the minor buccal salivary glands onto the mucosal surface. The environment experienced by a bioadhesive formulation *in situ* will, therefore, vary. It is of note that relatively weak bioadhesive formulations can be retained in the upper buccal pouch for extended periods [54], and so it is apparent that minimal dislodging stresses must exist there.

2.2 Formulations

Buccal bioadhesive drug delivery systems include tablet, patch, semisolids/liquids and particulates. A whole range of these formulations has been reported over the last 20 years [5,9,55], but comparatively few have found their way onto the market.

2.2.1 Buccal tablets

These are solid dosage forms prepared by the compression of powder mixes that can be placed into contact with the oral mucosa and allowed to adhere. They can deliver drug multidirectionally into the oral cavity or to the mucosal surface. Alternatively, the presence of an impermeable layer can ensure that drug is delivered unidirectionally. For systemic therapy, they will hold a drug in intimate contact with its absorbing surface, offer some protection to enzymatic degredation and avoid first-pass metabolism. For local therapy, the formulation can be applied directly to a specific region. Disadvantages of buccal tablets can include patient acceptability (mouth feel, taste and irritation) and the nonubiquitous distribution of drug within saliva for local therapy [10-12]. A typical bioadhesive formulation consists of a bioadhesive polymer (such as polyacrylic acids or a cellulose derivative), alone or in combination, incorporated into a matrix containing the active agent and excipients, and perhaps a second layer to allow unidirectional drug delivery. Commercially available examples of these formulations are Suscard Buccal® (Pharmax; a matrix containing modified hydroxypropylmethylcellulose for the delivery of glyceryl trinitrate), Buccastem® (Reckitt Benckiser; a matrix containing xanthan and locust bean gums for the delivery of prochlorperazine) [9], Aphtach® (Teijin; a double-layered tablet with the drug triamcinolone incorporated into a hydroxypropylcellulose



A Polyacrylic acid
R = Allyl sucrose or allyl pentaerythritol (carbopols), or divinyl glycol (polycarbophil)

B Chitosan

C Cellulose derivatives
For example; sodium carboxylmethylcellulose
R_1, R_4 = CH_2OH; R_2, R_3, R_5 = OH;
R_6 = $OCH_2CO_2^-Na^+$
hydroxypropylmethylcellulose
R_1 = CH_2OCH_3; R_2 = OH,
R_3 = $OCH_2CHOHCH_3$; R_4 = CH_2OH; R_5, R_6 = OCH_3

Figure 2. The structures of some common bioadhesive polymers.

and carbomer adhesive matrix) [56] and Striant® (Columbia Laboratories; a buccal tablet containing the bioadhesives polycarbophil, carbomer and hypromellose for the delivery of testosterone). Over the last 20 years a range of such adhesive tablet formulations have been described in the literature and some recent examples are given in **Table 1**.

2.2.2 Films and patches

Patches are usually prepared by casting a solution of the polymer, drug and any excipients (such as a plasticiser) on to a surface and allowing it to dry. Patches can be made ≤ 10 – 15 cm^2 in size but are more usually 1 – 3 cm^2 with perhaps an ellipsoid shape to fit comfortably into the centre of the buccal mucosa [68]. In a similar fashion to buccal tablets, they can be made multidirectional or unidirectional (e.g., by the application of an impermeable backing layer). They have many of the advantages and disadvantages of buccal tablets, but by being thin and flexible, tend be less obtrusive and more acceptable to the patient. The relative thinness of the films, however, means that they are more susceptible to overhydration and loss of the adhesive properties. Dentipatch® (Noven Pharmaceuticals), a modified transdermal patch using Dot Matrix® technology (Noven Pharmaceuticals) and silicone as the adhesive for the delivery of lidocaine, Oradisc® (Access Pharmaceuticals), a multilayered patch for the delivery of amlexanox and BEMA® technologies (Atrix Laboratories), a bioerodible mucoadhesive disc, are examples of commercial products. Some recent examples of bioadhesive patches described in the literature are given in **Table 2**.

2.2.3 Particulates

These are typically delivered as an aqueous suspension but can also be applied by aerosol or incorporated into a paste or ointment. Particulates have the advantage of being relatively small and, therefore, more likely to be acceptable to the patient. However, the dose of drug retained on the buccal mucosa and, therefore, delivered may not be consistent relative to a single-unit dosage form such as a patch or buccal tablet.

Polymeric microparticles (23 – 38 µm) of Carbopol® (Noveon), polycarbophil, chitosan or Gantrez® (ISP Corporation) [73] were capable of adhering to porcine oesophageal mucosa, with particles prepared from the polyacrylic acids exhibiting greater mucoadhesive strength during tensile testing studies whereas, in 'elution' studies, particles of chitosan or Gantrez were seen to persist on mucosal tissue for longer periods of time [74].

Table 1. Some recently described (within the last 5 years) bioadhesive buccal tablet formulations.

Type of formulation	Bioadhesives	Active agent (and other major components)	Details
Drug reservoir incorporated into hollow in the surface of adhesive tablet [34]	Carbomer and HPC	Ergotamine	Absorption from buccal tablet more effective than oral administration in guinea-pigs
Nanoparticles incorporated into a rapidly disintegrating pellet [57]	Polyacrylamide	Insulin	Produces a significant reduction in blood glucose in anaesthetised diabetic rats
Bilayer tablet; bioadhesive layer and inert upper layer [58]	Polyoxyethylene	Cyanocobalamin	Buccal tablet gave higher bioavailabilities than a capsule preparation in dogs
Matrix [59]	Polyoxyethylene	Chlorpheniramine	Stayed in place in dogs for 4 – 24 h
Matrix [60]	Sodium alginate, HPMC	Omeprazole, (magnesium oxide)	*In vitro* study indicated bioadhesive properties and stability in saliva
Matrix [61]	Carbomer, HPMC	Carbamezepine	Some irritation observed on application, little drug absorption found even in the presence of an enhancer
Matrix [62,63]	Freeze-dried palmitoyl glycol chitosan	FITC dextran, denbufylline	Could be loaded with high levels (27.5%) of the model macromolecule and allowed the delivery of a small molecule in anaesthetised rabbits for a period of over 5 h
Matrix [64]	Carbomer and corn starch	Chlorhexidine	Less effective than mouthwash in reducing plaque formation
Matrix [65,66]	Starch-polyacrylic acid grafted copolymers	Testosterone/theophylline	Allowed testosterone delivery for 5 – 13.5 h *in vivo* in dogs and a slow release of theophylline *in vitro* over 3 – 6 h and retained *in vivo* in dogs for 2 – 3 days
Matrix [52]	Thiolated polycarbophil		*In vitro* more was bioadhesive and disintegrated less rapidly than the original polymer. It was also able to reduce enzymatic degradation
Matrix [67]	HPMC/carbomer	Danazol	Cyclodextrin added to promote drug release. A 25% bioavailability found *in vivo*

FITC: Fluorescein isothiocyanate; HPC: Hydroxypropylcellulose; HPMC: Hydroxpropylmethylcellulose.

2.2.4 Semisolids

These typically contain a bioadhesive polymer and drug plus any required excipient dissolved or suspended as a fine powder in an aqueous or non-aqueous base, depending on their solubility and concentration. They can be applied using the finger (or syringe) to a target region and tend to be more acceptable in terms of mouth feel to patients relative to a solid dosage form. However, they may deliver variable amounts of active ingredients in comparision with a unit dosage form. Commercial examples are Adcoryl in Orabase® (Bristol-Myers Squibb), an ointment containing triamcinolone acetonide in a pectin-, gelatin- and carboxymethylcellulose-containing ointment base and Bioral gel® (Merck), carbenoxolone in a carboxymethylcellulose-containing ointment base. Some recent formulations are given in **Table 3**.

2.2.5 Liquids

Liquids have the advantage of being readily distributed throughout the oral cavity (e.g., as mouthwashes) but are not readily retained or targeted to the buccal mucosa, and would deliver relatively uncontrolled amounts of an active ingredient.

Patel and colleagues [82] found that polymers will adsorb from solution on buccal cells *in vivo*. From the wide range of polymer solutions screened, chitosan gave the greatest binding, followed by methylcellulose, gelatin, Carbopol 934P and polycarbophil. Binding was confirmed using atomic force microscopy [83], and binding for ≥ 1 h was found in human volunteers [84] after rinsing with a solution of this polymer. The adsorption of crude aqueous extracts of various herbs such as *Fucus vesiculosus* and *Calendula officinalis* from solution onto pig buccal mucosa *in vitro* has also been described [85].

Table 2. Some recently described (within the last 5 years) bioadhesive patches and films.

Bioadhesives	Active agent (and other major components)	Details
Ethyl hexyl acrylate/acrylic acid copolymer [69]		Hydration rate reduced, mucoadhesive force greater with these films than with polyacrylic acid alone
Vinyl acetate/PVP copolymers [101]		Drug and excipients (plasticisers, flavouring agents) can be included, may remain adhesive for ≤ 24 h
Polyacrylic acid, PVP and carmellose with a cellulose derivative (HPMC) [102]	Anti-inflammatory or steriod	Two-layered device, bioadhesive layer cast onto hydrophobic layer
Carmellose, alginate, methylcellulose [70]	Terbutalene	Bioadhesive layer cast onto polyglassine
Carbomer and chitosan complexes [71]	Acyclovir	Intermacromolecular complexes were advantageous in retention and drug-release studies
Chitosan, polyvinylalcohol, HPMC and PVP [72]	Miconazole	The polyvinylalcohol/PVP patch gave the best release profile, and allowed drug release over 6 h in human volunteers

HPMC: Hydroxypropylmethylcellulose; PVP: Polyvinylpyrrolidone.

Table 3. Some recently described (within the last 5 years) semisolid formulations for buccal drug delivery.

Type of formulation	Bioadhesives	Active agent (and other major components)	Details
Gel [75,76]	Hydroxyethylecellulose, PVP, polycarbophil	Chlorhexidene, flubiprofen	*In vivo* study: inflammation reduced on daily application of flubiprofen-containing formulation
Gel [77]	Polymethylvinyl-ether-co-maleic anhydride and PVP		Polymers were bioadhesive showing rheological synergy
Gel [78]	Poloxomer 407/carbomer	Triamcinolone acetonide	In rabbits, gel delivered a constant amount of drug, which increased with an absorption enhancer
Gel [33]	Pluronic	Insulin (fatty acids)	In anaesthetised rabbits, incorporating an absorption enhancer, enhanced and prolonged absorption occurred
Gel [79]	Eudispert hv	rgEGF	Increased healing rate of ulcers in hamster buccal mucosa
Ointment [80]	Polymethacrylamide	Benzyl nicotinate	Effective drug delivery to rat mucosa
Gels [81]	Hexadimethrine	Triclosan	Anionic cyclodextrin complexed with bioadhesive retention on buccal mucosa allowing prolonged release

HPMC: Hydroxypropylmethylcellulose; PVP: Polyvinylpyrrolidone.

2.3 Lectins

Lectins are proteins or glycoproteins that bind to specific sugar residues [86], and can, therefore, interact with the glycoconjugates including those present on cell surfaces or the mucins in the salivary pellicle. This provides the opportunity for their use to anchor a delivery system onto the oral mucosa or a mucosal lesion [87]. Smart and colleagues [88] found that the lectins from *Arachis Hypogaea, Canavalia ensiformis* and *Triticum vulgaris* bound to oral mucosal cells, the latter showing the greatest binding (calculated to be ~ 7×10^9 molecules/cell). In an *in vivo* study in rats, the *T. vulgaris* lectin showed the greatest levels of retained lectin after 30 min (~ 30 mg) on the buccal mucosal tissue and was still detected at similar levels after 2 h.

2.4 Toxicity and irritancy

Formulations that produce local damage at the site of application, such as ulceration of the mucosa, would preclude their widespread usage as a result of the associated pain and discomfort. This is particularly important in buccal drug delivery where the formulation is in contact with the mucosa for extended periods [89].

Toxic effects can arise from the drug itself, the bioadhesive or from other components of the formulation. For example, carbomers have been reported to produce mucosal irritation [90] believed to result from a localised low pH [91], whereas lectins have been shown to be cytotoxic [92]. Excipients such as absorption enhancers (e.g., sodium dodecyl sulfate) have also been reported to be irritant [22].

3. Expert opinion and conclusions

The buccal route using bioadhesive formulations has apparent attractions as an alternative to oral administration for delivering drugs into the systemic circulation, as well as for local drug therapy. This route is readily accessible and avoids first-pass metabolism. However, the fact that there are comparatively few formulations available commercially that exploit this method of administration indicates that there are still some major barriers to overcome. Most patients will probably prefer to take a tablet or capsule orally wherever possible, unless there is a distinct advantage to administration via the buccal route. Taste, mouth feel and possible mucosal irritation are important issues for patient acceptability; it is easy to understand how the 'sticky' buccal tablet or patch (described in many papers such as [34,60,61,67]) slowly releasing an unpleasantly flavoured drug may not be considered an acceptable experience by a patient. For the pharmaceutical scientist the relative impermeability of the oral mucosa (especially to large biopharmaceuticals), the variable challenges within the oral cavity (such as food consumption and salivary washout) and the fact that a 'high-technology' formulation is likely to be swallowed by the patient provide major additional challenges. There have not been a shortage of proposed formulations for buccal drug delivery in the literature over the last 20 years but the conversion of these to actual commercial products remains limited. In order to further advance the use of buccal drug delivery, a 'technology leap' is probably required, using more effective bioadhesives in new, more efficient and patient-friendly delivery systems. However, the drugs that can be delivered by this route may remain limited and, for the systemic delivery of large molecules, a modification of the technology used to enhance transdermal drug delivery may prove to be most appropriate.

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Patents

101. ADIR ET COMPAGNIE FRANCE: US5900247 (1999).

102. ACCESS PHARMACEUTICALS, INC., USA: US6585997 (2003).

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