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Review Article

Theme: Pediatric Drug Development and Dosage Form Design
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Buccal Dosage Forms: General Considerations for Pediatric Patients

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ABSTRACT. The development of an appropriate dosage form for pediatric patients needs to take into account several aspects, since adult drug biodistribution differs from that of pediatrics. In recent years, buccal administration has become an attractive route, having different dosage forms under development including tablets, lozenges, films, and solutions among others. Furthermore, the buccal epithelium can allow quick access to systemic circulation, which could be used for a rapid onset of action. For pediatric patients, dosage forms to be placed in the oral cavity have higher requirements for palatability to increase acceptance and therapy compliance. Therefore, an understanding of the excipients required and their functions and properties needs to be particularly addressed. This review is focused on the differences and requirements relevant to buccal administration for pediatric patients (compared to adults) and how novel dosage forms can be less invasive and more acceptable alternatives.

KEY WORDS: buccal delivery; mucoadhesion; pediatric dosage forms; pediatric films; pediatric tablets; transmucosal.

INTRODUCTION

Due to the demand for safe and effective delivery systems for pediatric patients, experts have to develop new dosage forms adapted to their special needs. The "pediatric" term encloses several groups of age including newborns (0–27 days), infants (28 days–23 months), children (2–11 years), and adolescents (12–17 years), resulting in differences during their physiological development that could impact dosage form development (1).

For the pediatric patient population, the oral route of administration is the most popular due to many advantages including ease of administration, patient compliance, and well-validated and scalable manufacturing methods (tablets, capsules, and liquid dosage forms) (2). Regardless of these advantages previously mentioned, many patients have difficulties with solid dosage forms due to swallowing, and even some pediatric patients (depending on the age group) are not able to swallow solid dosage forms due to their undeveloped motor and also cognitive skills (1). As another route for pediatric patients, rectal administration is an adequate alternative and also in other conditions such as vomiting and nausea (3). The rectal route encompasses many dosage forms such as suppositories, creams, enemas, and ointments, but administration often becomes more uncomfortable to patients as they age.

Parenteral routes accessed through injections are alternative routes chosen in case of emergencies, when a quick onset of action is needed or when the drug cannot be formulated for the oral route. However, a number of limitations for injectables can be identified, including the need for trained professionals for administration, the invasiveness of the process, the risk of blood-borne infections, and injury and pain related to injections, especially for pediatric patients (4).

In order to avoid the shortcomings of the oral and injectable routes for pediatric patients, alternative administration routes have been researched and developed, including the sublingual, buccal, nasal, pulmonary, and transdermal among others. In the oral cavity, oral mucosal administration consists mainly of two routes: the sublingual route or buccal route (5). Both epithelia can allow for drug diffusion to reach the systemic circulation and are attractive for pediatric patients due to their acceptance without the need for injections or the swallowing of solid dosage forms. Furthermore, the oral mucosal routes present advantages such as bypassing the gastrointestinal tract (GIT) and avoidance of the hepatic first pass metabolism (6,7). Additionally, the

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buccal epithelium has abundant blood flow and relatively high permeability (2,8,9), which is key when a fast clinical response is required. For example, in events of tolerance to opioids for the treatment of cancer-associated pain (5), the use of a buccal fentanyl film can quickly provide pain relief (10).

Several buccal formulations have reached the market for adults (Actiq, Belbuca, Bunavail, Dentipatch, Fentora, Onsolis) (2,11–13); however, pediatric buccal delivery is still not well explored. A number of limitations including differences in physiological development, toxicity, and formulation challenges restrain pediatric buccal dosage form development. In this review, we cover relevant aspects of the anatomy and physiology of the buccal epithelium with a focus on pediatric patients. We then continue to review buccal dosage forms researched for pediatric patients and highlight film formulations and their critical excipients, as better candidates for development.

PHYSIOLOGICAL ASPECTS OF THE PEDIATRIC ORAL CAVITY

Anatomy and Physiology

A variety of tissues can be found inside the oral cavity including the lips, cheeks, tongue, hard and soft palate, and the floor of the mouth (9). All these different epithelia, according to physiological and pathological conditions, will directly affect the drug permeability. Blood irrigation, epithelium thickness, cell keratinization, and the presence of enzymes, among other factors, can impact the permeation potential of drugs through the oral mucosa (4). In general terms, three types of oral mucosa have been identified in the oral cavity with similar distribution in both adults and children (1): lining mucosa (60%), masticatory mucosa (25%), and specialized mucosa (15%). The lining mucosa comprises the non-keratinized sublingual and buccal epithelium. The masticatory mucosa comprises the hard palate and gums (both keratinized). Finally, the specialized mucosa, exhibiting both keratinized and non-keratinized regions, is found in the dorsal surface of the tongue (4).

From a drug delivery standpoint, the buccal mucosa offers advantages over other epithelia in the oral cavity including a larger surface area (50.2 ± 2.9 cm^2) (14) and an intermediate permeability compared with the low permeability of gingival and palatal epithelia (15). Furthermore, the buccal epithelium is highly vascularized and any drug diffusing across the buccal mucosa can directly access systemic circulation *via* capillaries and venous drainage, bypassing the hepatic first pass metabolism (16). The buccal mucosa is composed of an outer layer corresponding to the upper quarter or third of stratified squamous epithelium on top, followed by a basal membrane, lamina propria, and a submucosa as its innermost layer (Fig. 1) (4,17,18). The main function of this epithelium is to protect the underlying tissue, either from any potential harmful agent or fluid loss (9).

This buccal epithelium is similar to the rest of the squamous epithelia in the body, where a continuous desquamation from the surface occurs by a homeostasis process between cell differentiation and cell flaking. The buccal epithelium can heal quickly after damage due to this homeostasis (19). This constant cell differentiation and stratification affect the permeability of the epithelium, making the buccal mucosa more permeable than the skin but less than the intestine (6,20). Furthermore, the sublingual mucosa, smaller in area for administration but thinner than the buccal mucosa, has higher permeability and it is more suited for a rapid onset of action. Thus, due to its mechanical and environmental conditions, sublingual administration is limited by the short duration of action achieved (17).

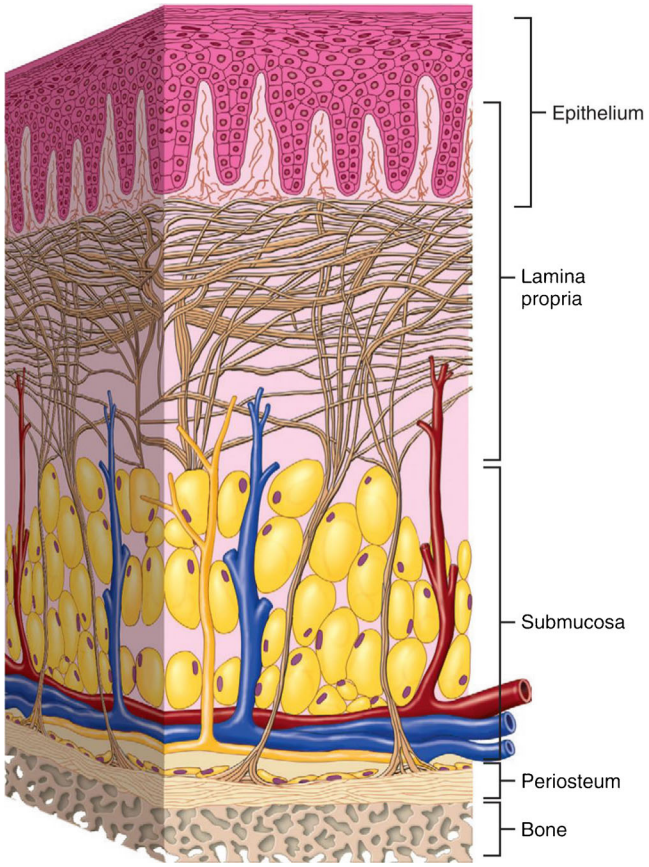

Fig. 1. Representation of the buccal mucosa. Reproduced with permission from Nanci (18)

Many studies have shown that the outer cell layers (upper third of the epithelium) are the main barrier against molecules permeating due to the relative large amounts of lipids in the intercellular spaces of the epithelium surface (6,19,21). Those lipids are originated from extrusion of the content of the so-called membrane coating granules, making this outer layer a limiting step in penetration through the mucosa (22). Keratinized areas of the oral cavity (gums and palate) have a larger content of cholesterol and ceramides (much like the skin), whereas non-keratinized domains such as the buccal and sublingual mucosa have a greater presence of phospholipids, esters of glycosylic ceramides, and cholesterol (lipid with polar character). This accounts for the main differences in permeability between these tissues in the oral cavity (21).

Another contributing factor to the permeation properties of a drug across the buccal epithelium is the physicochemical properties of the compound (23). As described above, two main domains for transport can be identified across the buccal

epithelium, *i.e.*, lipophilic in the cell membrane domain and more hydrophilic in the extracellular space; therefore, two pathways are described, namely the paracellular and transcellular routes (Fig. 2). The paracellular route is observed mostly for hydrophilic substances, while lipophilic molecules would exhibit poor solubility and thus diffuse transcellularly (17,19,24).

In relation to the physiologic changes generated from childhood to adulthood, as we get older, there is a decrease in the thickness of the epithelium (25); furthermore, studies in animals have shown that during aging there is a decrease on cell density (26) and a decrease on the mitotic cell activity (27). Moreover, a study in humans by Eid *et al.* (28) has found that the area and perimeter of epithelial cells become larger, suggesting that the cells become flatter with age. Despite these differences, through the development of buccal mucosa, aging does not significantly affect the irregularities that present the epithelial connective tissue interface over the range of nine decades of life (28).

Saliva and Mucin

Saliva is a fluid composed mainly of water (99%) (17,29) and has several protective functions, such as lubrication, moistening, and adaptive and innate immune activities (30). This fluid is produced by three major types of glands: the parotid, submandibular, and minor salivary glands (31). Within the non-water 1%, several organic molecules can be found such as enzymes (where the most important is amylase responsible for starch digestion) (27), antimicrobial substances such as immunoglobulins (IgA, IgM, and IgG) (30,32), lipids, small organic molecules such as glucose or urea, and electrolytes (sodium, calcium, chloride, and phosphates) (33).

The most important factor when assessing the influence of saliva in buccal formulations is the saliva flow rate, which directly affects the extent of drug retention on the absorption site. Sonesson *et al.* found that the saliva flow rate in 3-year-old children was lower than of adults (34), which may be problematic for the formulation of mucoadhesive buccal dosage forms as hydration and swelling are required for proper performance (35). For buccal dosage forms, there is a balance between hydration for mucoadhesion and undesired drug swallowing; thus, an increased saliva flow rate may produce a premature drug swallowing or swallowing of the whole dosage form and therefore a reduction in drug buccal bioavailability (2). This is known as the "saliva wash out effect" (36) and could result in a non-uniform drug distribution in saliva, which may result in lower amounts being absorbed by the mucosal tissues and subsequently result in variable systemic bioavailability (37).

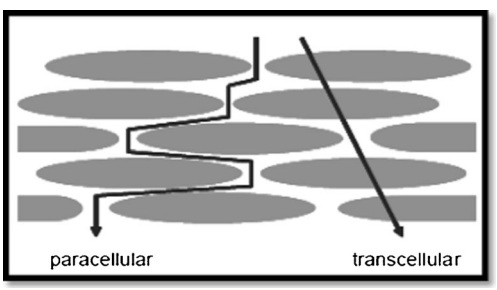

Fig. 2. Representation of paracellular and transcellular route. Reprint with permission from Ehrhardt and Kim (22)

The mean pH of all sites of oral mucosa in adult is 6.78 ± 0.04, with significant differences between mean pH values in the different tissues, like in the palate (7.34 ± 0.38), the floor of the mouth (6.5 ± 0.3), and in the buccal mucosa (6.28 ± 0.36) (38). The pH value has an important role on the diffusion of the ionized form of drugs (2). In healthy pediatric patients, a slightly lower pH 6.64 ± 0.44 has been described as the mean of all sites comprising the oral mucosa, which is variable depending on disease/disorder state or medication (Table I) (31).

Additionally, drastic changes in buccal pH, due sometimes to formation of plaque in teeth and subsequent caries (39), may result in drug dissolution issues (40). Psoter *et al.* have reported that these conditions of drastic changes in pH in malnourished children resulted in a decrease in saliva (in 10% of children) (41). It has been conventionally thought that the saliva flow rate in children can be altered by drugs, making oral health status decline and resulting in caries. However, a recent study on the administration of methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in 5–17-year-old pediatric patients found that unstimulated whole saliva flow (USF) levels in ADHD were lower than that observed in pediatric patients without ADHD. In the ADHD group, there were no differences in USF levels between those who received and did not receive medication for ADHD. The similarity in USF between the two ADHD groups refutes the claim that methylphenidate may cause mouth dryness (xerostomia) in children, and further studies should be conducted to corroborate this finding (31) (Table II).

Saliva also has an important role in immunity; for example, glycoprotein 340 and sialic acid are common terminal structures of mucus glycoproteins that interact with microorganisms as well as free radicals (30) being a barrier against potential harm. The minor salivary gland secretes around one third of all IgA found in saliva. This immunoglobulin (IgA) is the major adaptive immune protective mechanism in saliva, besides different types of mucin. Due to the immune system maturation, the IgA concentration increases from childhood to adulthood (30,42).

The most relevant biomacromolecule in the buccal mucosa is mucin, an amphoteric glycoprotein containing a large amount of carbohydrates (70–80%) (4,40). In the buccal mucosa, mucin molecules are entangled and form a cohesive gelatinous layer with a thickness ranging from 40 to 300 μm

Table I. Average pH Values of the Oral Mucosa of Adults, Children, ADHD Non-Medicated Children, and ADHD Medicated Children (31,38)

	pH (mean oral mucosa)
Adult	6.78 (0.04)
Children	6.64 (0.44)
ADHD non-medicated children	6.45 (0.49)
ADHD medicated children	6.43 (0.42)

ADHD attention deficit/hyperactivity disorder

Table II. Mean Unstimulated Whole Saliva Flow (USF) Values (mL/min) for 5–17-Year-Old Pediatric Patients (31)

Number of subjects	Number of subjects	Mean USF (mL/min)
ADHD non-medicated group	31	0.72 (0.33)
ADHD medicated group	30	0.85 (0.53)
Control group	30	1.13 (0.70)

Data expressed as means (standard deviation)
ADHD attention deficit/hyperactivity disorder

constituting a barrier for drug diffusion though the buccal epithelium (43). Also mucin can self-aggregate contributing to the viscous of the whole mouth saliva. The viscosity is important to wet food with different properties (hydrophobic or hydrophilic) and maintain the food particles stick together (29). In normal oral cavity pH, mucin is negatively charged due to its sialic acid and sulfate residues. Furthermore, mucoadhesive dosage forms rely on polymer-mucin interactions to adhere and prolong the time for release and absorption (see section "Mucoadhesive polymers") (2). The literature has identified two different structures of mucin in saliva, high molecular weight mucin glycoprotein (MG1) and low molecular weight mucin glycoprotein (MG2). MG1 has a low quantity of proteins (14.9) and is bound by disulfide linking creating a semipermeable barrier in the mucosa surface (44). MG2 has different sizes depending on the saccharide that contains ranging from disaccharides to heptasaccharides.

Besides the importance of mucin in mucoadhesion, it also has a role in immune response. As salivary mucins have a carbohydrate sialic acid domain, they can bind lectin present in the surface of bacteria, leading to bacteria agglutination, and the inability of binding to the host tissue. This leads to the potential immune role that mucin plays as a clearance system of bacteria in the oral cavity (44,45).

PHYSICOCHEMICAL PROPERTIES OF DRUGS RELEVANT TO PEDIATRIC PATIENTS

The dose determination for pediatric patients can be achieved through four different methods as depicted in guidelines: (A) the use of allometric scaling (for intravenous medication) suggests that the clearance can be escalated by the following formula: $(\text{body weight})^{0.75}$ (46). Clearance values obtained by scaling to body surface area do not require height measurement; (B) using the body surface area, which assumes a proportionality with physiological processes; however, the large number of formulas to calculate body surface area makes this estimation difficult and may lead to several errors but is more secure than body weight dosing (47); (C) normalization of a dose to body weight may have problems with pharmacokinetic parameters due to the differences in pediatric clearance that can be altered compared with adult clearance; the difference of this strategy with the allometric scaling is that this method does not consider factors such as obesity and differences in clearance for certain drugs to calculate the body surface area leading to a possible overdose (46); and (D) classifying the patient into an age-based category to see the recommended doses; however, these could result in a bad approach due to the pharmacokinetic variability (48). Knowing these four types of methods, the dose for a buccal administration can be calculated by methods B, C, and/or D but it has to be mentioned that to avoid all the potential errors mentioned above, it is imperative to extend the investigation and development of dosage forms, considering that pharmacokinetics are not the same over the range of ages enclosed in the "pediatric" term (49). For instance, the plasma concentration of pediatric patients can easily be four to five times higher than adults due to their small volume of distribution, heart rate, and reduced blood pressure (13,50).

For the pharmacokinetic problem mentioned above, the design and formulation of a drug to be administered in a buccal dosage form must consider ideal physicochemical properties. These ideal properties have been described as consisting of a solubility greater than 1 mg/ml, molecular size lower than 500 Da, lipophilicity with a log *P* greater than 10 and less than 1000, and a pK_a that favors the unionized form in the buccal pH, all of which would result in greater bioavailability (2,51,52).

Due to the limited amount of saliva and its variability in accordance to physiological conditions and regions in the oral cavity, solubility-limited drugs require particular formulation efforts for successful dosage form development. On the other hand, drug lipophilicity must be sufficient for the molecule to penetrate through the stratified epithelium of the mouth, containing large amounts of lipids such as phospholipids, cholesterol esters, ceramides, and glycosylic ceramides (17,21). Ideally, drug molecular weight needs to be small (below 500 Da) (2) since large molecules present difficulties to permeate through either the paracellular or transcellular route (*e.g.*, proteins and peptides) (53). Regardless of these limitations for large molecules, their formulation has been addressed by the use of permeation enhancers and mucoadhesive dosage forms (2,19).

DOSAGE FORMS FOR BUCCAL PEDIATRIC FORMULATIONS

Patient acceptability of a dosage form is a key aspect in the development of medicines for pediatric patients. For this purpose, taste and smell are highly relevant factors in formulation development (54). Many dosage forms designed for adults, such as buccal tablets, gels, and films, would also benefit children if they contained an appropriate pediatric dose (55). There are a large number of buccal dosage forms reported in past decades, but only a limited number of these have reached the market (56).

Liquid Dosage Forms

Liquid solutions or suspensions are preferred for pediatric patients because liquids decrease the potential risk of choking associated with swallowing solid dosage forms (57). Nonetheless, their biggest limitation is that they are not easily retained in the oral cavity and, if intended for buccal absorption, may result in swallowing before transmucosal absorption can take place (4). The dose and volume of liquid medicines may be limited by the solubility of drug substances; this problem may require the addition of cosolvents or

surfactant excipients in the formulation. It is important to mask unpleasant taste with sweeteners and flavors. If this is not achievable, sophisticated formulation approaches such as encapsulation of drug particles may be required (55).

A study of convulsive status epilepticus children compared a buccal midazolam solution with a rectal liquid diazepam, as a common neurological SOS medicine in the treatment of seizures (58). For the buccal administration, the authors loaded in a syringe an amount equivalent to 10 mg of midazolam and squirted the solution around the buccal epithelium. The diazepam (10 mg) rectal administration was performed using a commercial rectal tube. Midazolam buccally administered stopped 30 of 40 seizures in children, while rectal diazepam stopped 23 of 39 seizures (58). The study did not found significant differences in efficacy, time from arrival of the nurse to drug administration, time from administration to end of seizure, or total seizure length. These factors showed that buccal midazolam had clear practical and social advantages over rectal diazepam, considering that seizures can occur in public places (58). Another study confirmed that buccal liquid midazolam was a safe and consistently effective rescue therapy that often prevented the need for hospital admission (59). While numerous antiepileptic drugs have been used in convulsive status epilepticus, benzodiazepines tend to be preferred due to their swift therapeutic action and efficacy. In their study, Khan *et al.* showed that 91% of carers found that buccal midazolam was always, or usually, effective in terminating seizures (59).

Tablets

Several mucoadhesive tablet formulations have been developed in recent years for local or systemic drug delivery. For transmucosal delivery, tablets are placed onto the mucosal surface and need to elicit excellent mucoadhesive properties when in contact with saliva and the epithelium (51). They are designed to release the drug unidirectionally (towards the mucosa) or multidirectionally (buccal mucosa and oral cavity). However, their size is a limitation for the intimate contact with the mucosa surface and can be uncomfortable for children (60).

Effervescent Buccal Discs

Effervescent buccal discs are flatter, less thick than buccal tablets or conventional effervescent tablets and result in faster drug release. Jaipal *et al.* showed that the carbon dioxide released from buccal effervescent discs upon contact with saliva acts as a permeation enhancer (compared to non-effervescent discs) (61). Although this is an attractive alternative for pediatric patients due to the increased bioavailability effect, further investigations are required to assess the safety of this dosage form.

Lozenges

Lozenges are solid dosage forms intended to dissolve or disintegrate slowly in the mouth. They contain one or more drugs usually in a flavored and sweetened formulation. Lozenges come with an applicator to facilitate patient administration and dosing. Patients have to place the dosage form between the cheek and gum and suck on the medicine to start the release (62). Conventional lozenges produce a high initial release of drug in the oral cavity which rapidly declines to sub-therapeutic levels; thus, multiple administrations are possibly required (60). The dissolution and disintegration of the drug contained in the lozenges are controlled by the patient and depend on the frequency and intensity of sucking on the dosage form (4). The main limitation of lozenges is that the sucking process stimulates the production of saliva, which could result in a higher and uncontrolled swallowing, leading to a modification of the pharmacokinetics (drug may or may not be absorbed *via* the gastrointestinal route and alter bioavailability).

Films

Mucoadhesive films are retentive dosage forms that release drug directly towards the buccal epithelium and have gained relevance in the pharmaceutical industry as patient friendly and convenient products. Due to their small size (1–3 cm^2) and thickness (no more than 1 mm) (37), these dosage forms are more tolerable for patients, thereby improving therapy compliance (6,63). However, their limited dimensions also pose a challenge in the maximum amount of drug that can be incorporated.

Khan *et al.* have developed a buccal film formulation for pediatric drug delivery of omeprazole using aqueous and ethanolic films of hydroxypropyl methylcellulose (HPMC), carrageenan (CA), sodium alginate (SA), and methyl cellulose (MC). In order to stabilize omeprazole in water, L-arginine was added to the formulation. The authors found that HPMC films (Metolose 65 SH-50, HPMC 50 cP) were a potential choice for pediatric buccal administration due to the polymer hydrophilic nature, safety, flexibility, transparency, toughness, uniformity, and ease of peeling (56).

In another alternative use of films as buccal delivery systems, Cui *et al.* developed a buccal vaccine and characterized its potential in a rabbit animal model, evaluating two antigen proteins (β-galactosidase and plasmid DNA-expressing β-galactosidase) loaded in bilayer films. The antigen effect was measured by detecting the presence of IgG in rabbit (induced antigen specific), which was confirmed by ELISA. The positive ELISA for both antigens and therefore the presence of IgG after the administration of the buccal bilayer films in rabbit buccal mucosa indicated that the buccal route could be a potential route for immunization (64). The possibility for pediatric patients buccal immunization could decrease the safety problems related to the use of needles (trained professionals for administration, the risk of blood-borne infections, and injury and/or pain) (4,64) and result in a more comfortable patient-friendly dosage form. However, further research is needed to determine its real potential.

EXCIPIENTS

One of the problems for buccal administration to pediatric patients is the acceptability of a dosage form, which impacts directly in therapy compliance. Therefore, assessing palatability is highly relevant when developing pediatric dosage forms, and excipients are key in improving

organoleptic properties (65). The following sections will review common excipients used in buccal formulations such as mucoadhesive polymers, penetration enhancers, and organoleptic adjusting agents.

Mucoadhesive Polymers

Mucoadhesive polymers are not only capable of increasing the contact time and drug delivery, but also due to the intimate contact that the polymer has at the site of absorption (oral mucosa), they can prevent potential drug degradation by enzymes present in the mucosal surface (66,67). The therapeutic use of mucoadhesive drug delivery systems was recognized in the early 80s when Nagai *et al.* showed the influence on bioavailability after administration of a viscous mucoadhesive tablet intended for the oral cavity (68).

In the past two decades, industry and academia have developed extensive research in mucoadhesive polymers, which has yielded a better understanding of the mechanisms of action involved. Among the most frequently used polymers we can find poly(acrylic) acid derivatives that act by forming a large number of hydrogen bonds with mucin (35,69,70). Polyvinylpyrrolidone is another widely used mucoadhesive that has the advantage of high stability at a large pH range (71), which is of particular relevance for the development of pediatric dosage forms. Table III depicts a review of widely used polymers for buccal dosage forms.

Chitosan, a widely investigated natural polysaccharide, is well known for its biodegradable, non-toxic, and mucoadhesive properties (73,84–91) but has yet to be used in a product approved by the FDA for its use on dosage forms (4). Moreover, chitosan has not been evaluated in terms of efficacy and safety in buccal administration for pediatric patients.

The most recent next-generation mucoadhesives are thiolated polymers. These new polymers have thiol derivatives throughout the polymeric chain that when in contact with mucosa form disulfide covalent bonds with mucus glycoproteins, resulting in superior mucoadhesion compared with conventional polymers (92,93). However, their safety and potential in children need to be further investigated.

Penetration Enhancers

Penetration enhancers (also known as absorption or permeation enhancers) are chemical substances that have the ability to increase the rate of permeation of a drug through a biological membrane when co-formulated in a dosage form (51). According to the literature, buccal penetration enhancers exert their effect by a different mechanism to that commonly associated to skin absorption (2,24,94–97). Conversely, buccal penetration enhancers act by increasing drug partition in the oral epithelium and/or extracting intercellular lipid domains, as well as increasing the drug retention time on the surface of buccal mucosa. Furthermore, they can also act by an interaction with epithelial proteins. Understanding the path of drug absorption will determine the choice of a specific enhancer (24). The most studied buccal penetration enhancers are described in the sections below, with a proposition of their mechanism and limitations of each; however, many still need to be evaluated for their potential toxicity in pediatric patients.

Table III. Widely Used Mucoadhesive Polymers for Buccal Administration

Mucoadhesive polymer	Relevant properties
Chitosan	Natural polymer Soluble in acid solutions Cationic polymer Biodegradable High mucoadhesive properties (2,72,73)
Hydroxyethyl cellulose (HEC)	Semisynthetic and water soluble (temperature range 0–38°C) (2) Non-ionic polymer, fast rate of erosion, and high swelling (74) Chance for zero-order drug release kinetics (74)
Hydroxypropyl cellulose (HPC)	Semisynthetic, non-ionic, and water-soluble polymer Moderate swelling and slower rate of erosion compared with HEC (75)
Hydroxypropyl methylcellulose (HPMC)	Semisynthetic, non-ionic, and water-soluble polymer Rapid swelling, medium mucoadhesion, and chance for first-order drug release kinetics (76)
Guar gum and xanthan gum	Natural polymers Non-ionic Water-soluble polymers (77) High swelling (78)
Carboxymethyl cellulose (CMC)	Anionic polymer High swelling properties (79) High mucoadhesive properties (79)
Sodium alginate	Fast dissolution and erosion High swelling properties (66)
Poly(ethylene oxide)	Non-ionic polymer High mucoadhesive properties (80) with high concentrations of polymer (81) Zero-order release kinetics for cyclodextrine-loaded films (82)
Poly(vinyl pyrrolidone) (PVP)	Non-ionic (2) Improve elastic properties and film forming properties (83). High swelling properties (66)

Surfactants and Bile Salts

Bile salts and surfactants have been shown to improve the permeability of various compounds through the buccal mucosa, both *in vitro* and *in vivo* (24,98). Studies in pig as a buccal mucosa animal model have shown that the enhancing effects of surfactants are depicted when the critical micelle concentration (CMC) is exceeded (96). This suggests that the mechanism would be the lipid extraction due to micelle formation, which would decrease the barrier properties of the mucosa and thereby increase the permeability of drugs. On the other hand, it has been found that sodium dodecyl sulfate (SDS) maximizes drug penetration only through the paracellular pathway (97). SDS was not able to enhance the buccal permeation of estradiol (a transcellular permeating drug), but it was able to enhance caffeine permeation (a paracellular permeating drug). This indicates that, in fact, SDS promotes lipid solubilization but mainly from lipids found in the intercellular space. Therefore, the enhancing capacity of surfactants will depend directly on the drug route of absorption.

Lipid extraction is not the only mechanism by which surfactants can increase the permeability through the mucosa. In a study in rabbits where the permeability of salicylic acid was evaluated, it was suggested that sodium deoxycholate and sodium lauryl sulfate produced an unwinding and extension of the helicoidal protein structures, thus opening the polar way for diffusion (94).

Fatty Acids

Fatty acids improve the skin permeation of many drugs, which has been shown by differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) where increased intercellular lipid fluidity on skin tissue was identified (24). Particularly, DSC studies in porcine stratum corneum showed that the use of *cis*-11-octadecenoil acid resulted in a decrease in glass transition temperatures and sharpness of transitions (99). Additionally, FTIR studies showed changes in C-H band intensity and frequency in presence of *cis*-11-octadecenoil acid. The actual mechanism by which this effect is produced through the buccal epithelium has not been fully described, yet it is thought that this is due to a decrease in the structural order of the lipidic composition (95,100). The reason why the mechanism is not yet fully described could be the use of inadequate models (mucosa of rats for example, which is mostly keratinized) and the lack of a systematic study of the mechanism itself (6,95).

Chitosan

Nicolazzo *et al.* have attributed the enhancing effect of chitosan to mucoadhesion, which results in higher drug retention time on the buccal mucosa surface (24). In the buccal epithelium, tight junctions are uncommon compared with their relative quantity in the intestine (101), suggesting that the mechanism of action is different at the various mucosal surfaces. In addition to its mucoadhesive properties, chitosan acts in the buccal epithelium by disrupting the lipid organization (102), while at the intestine, epithelium chitosan acts by a charge-dependent effect, producing the opening of the tight junctions that leads to an enhancement in paracellular drug absorption (72).

In a preliminary study, Cid *et al.* developed chitosan gels for buccal delivery of celecoxib. In these formulations, a concentration of chitosan 3.0% was used as a penetration enhancer combined with 2–3% Azone (another penetration enhancer that acts by increasing the drug partition in the buccal mucosa). Studies in pig buccal epithelium showed a significant increase in drug retention at the buccal site by higher mucoadhesion and mucosa retention, acting as a depo for continuous and gradual drug absorption (103).

Cyclodextrins

Cyclodextrins are cyclic oligosaccharides, which can enhance permeation of a drug by improving its stability and availability in the surface of biological barriers. This has been attributed to the increase in thermodynamic activity of the drug in the vehicle and/or to an increase in dissolution rate. As drugs partition in cyclodextrins, there is a net increase in thermodynamic activity leading to an augmented concentration gradient, with the potential to promote absorption, thus increasing bioavailability (104,105). Such absorption enhancers have the advantage of keeping hydrophobic molecules in solution by forming an inclusion complex molecule—cyclodextrin (106). Another mechanism for permeation enhancement is due to lipid extraction by forming inclusion complexes with cell membrane lipids (107). A study has shown how dimethylated β-cyclodextrin at 2.5% and 5% helped increasing the amount of PEG-4000 transported across Caco-2 monolayers (108). Transephitelial electrical resistance (TEER) studies showed that this enhancing effect was elicited without damage to the cell monolayer.

Organoleptic Adjusting Agents and Other Excipients

As stated above, pediatric patients are defined over a wide range of age including newborns, infants, children, and adolescents, and this influences directly their capacity of handling different dosage forms. Liquid dosage forms are preferred for infants and children, but adequate sensorial properties are difficult to achieve in solutions or suspensions (109), and this lack of palatability is the main limitation associated to this dosage form. This is particularly relevant for buccal absorption where a prolonged contact time is required which could lead to patient rejection.

Frequently in dosage forms for children, colorants and sweeteners are required to increase acceptability (110). Some sweeteners include natural sugars as glucose, fructose, and sucrose; however, since buccal dosage forms are often intended to remain long periods in the buccal cavity, they may cause an acid pH favoring the appearance of caries (111,112). Therefore, artificial sweeteners such as aspartame, saccharin, and sucralose, among others are preferably used. Regardless of the use of either natural or artificial sweeteners, they are known to have a saliva-stimulating effect, which as we stated above may affect the drug absorption rate (31,113).

Some conventionally used excipients could also pose a threat to safety in pediatric patients. For instance, propylene glycol, a solvent used in the preparation of oral and injectable drugs, generally considered stable, pharmacologically inert,

and with a low systemic toxicity, has been reported to trigger toxic symptoms upon ingestion. Pediatric patients developed seizures associated with long-term ingestion of medication with propylene glycol as solvent. The episodes remitted when the ingestion of propylene glycol was discontinued (114,115). Another problematic excipient is benzyl alcohol, which may produce the "gasping syndrome" causing severe neurotoxic effects and brain damage to newborns. Moreover, when co-administered with diazepam, it may lead to death (116,117).

CONCLUSION

The buccal mucosa can be used as an alternative route for drug delivery to pediatric patients, yet the anatomical and physiological differences to adults and within the pediatric age group need to be considered during development. Buccal administration presents many advantages such as avoidance of first pass metabolism, fast onset of action, no need of swallowing, improved bioavailability, and potentially pediatric patient-friendly dosage forms (there is a lack of pediatric buccal dosage forms approved). Furthermore, buccal dosage forms are potential alternatives to invasive routes of administration (intravenous or subcutaneous route) for pediatrics and adults. Thus, buccal administration could have a direct impact in patient compliance by avoiding the pain associated with these invasive administrations.

Due to their high contact time with the mucosa, retentive mucoadhesive dosage forms can deliver drug more effectively than liquids. For the pediatric population, the formulation of a palatable buccal dosage form is imperative to gain acceptance and ultimately therapy compliance. Although many pediatric formulations still are in development, the use and selection of excipients should be evaluated in terms of palatability but also for safety and effectiveness for pediatric patients. A number of formulations evaluated in animal models or human adults still need to be assessed in pediatric patients. Safety and effectiveness studies for these formulations still are required to establish their potential use in pediatric medicine.

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