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Oral transmucosal drug delivery for pediatric use ☆

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ABSTRACT

The formulation of medicines for children remains a challenge. An ideal pediatric formulation must allow accurate dose administration and be in a dosage form that can be handled by the target age group. It is also important to consider the choices and the amount of excipients used in the formulation for this vulnerable age group. Although oral formulations are generally acceptable to most pediatric patients, they are not suitable for drugs with poor oral bioavailability or when a rapid clinical effect is required. In recent years, oral transmucosal delivery has emerged as an attractive route of administration for pediatric patients. With this route of administration, a drug is absorbed through the oral mucosa, therefore bypassing hepatic first pass metabolism and thus avoiding drug degradation or metabolism in the gastrointestinal tract. The high blood flow and relatively high permeability of the oral mucosa allow a quick onset of action to be achieved. It is a simple and non-invasive route of drug administration. However, there are several barriers that need to be overcome in the development of oral transmucosal products. This article aims to provide a comprehensive review of the current development of oral transmucosal delivery specifically for the pediatric population in order to achieve systemic drug delivery. The anatomical and physiological properties of the oral mucosa of infants and young children are carefully examined. The different dosage forms and formulation strategies that are suitable for young patients are discussed.

Contents

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1. Introduction

The development of formulations for pediatrics is a challenging field of research. Pediatric patients include newborns, infants, children and adolescents. The upper age limit used to define pediatric population varies among different countries, usually including adolescents up to 18 or 21 years of age. The different age groups have different physiological and pharmacokinetic consideration, and their ability to handle formulation is also vastly different [1,2].

Oral transmucosal drug delivery is an attractive route of administration to achieve systemic drug delivery for pediatric patients. Absorption of drugs across the oral mucosa can bypass hepatic first pass metabolism and similarly avoid drug degradation in the gastrointestinal tract. Because of the abundant blood flow to and the relatively high permeability of the oral mucosa, fast onset of drug action may readily be achieved [3,4]. This is particularly desirable during an emergency situation when a rapid clinical response is required [5]. It is also a useful route of administration during a state of patient unconsciousness, when swallowing is impaired. Compared to parenteral administration, delivery of drugs via the oral cavity is relatively simple and non-invasive. Medication can be easily administered by the parents or carers of young patient without special technical skills, although the cooperation of the patient is sometimes necessary. Oral cavity delivery may also avoid the risk of blood borne infections or injury associated with parenteral administration. In addition, the absence of needle administration and the pain associated with this can also improve compliance in young children.

A drug candidate should possess the necessary physicochemical properties before it is considered for oral transmucosal delivery development. These include good lipophilicity and water solubility at physiological pH, as well as high potency. In addition, the drug must not cause any local irritation in the oral cavity. Apart from the intrinsic drug properties, there should also be a clear clinical benefit in developing a product for this route of delivery. To achieve systemic drug delivery through the oral mucosa effectively, several physiological barriers presented by the oral cavity must be overcome, namely the intrinsic enzyme activity, the relative permeability of the oral mucosa and the small fluid volume for dissolution and absorption. A mucoadhesive drug delivery system is a commonly employed strategy to increase the contact time of formulation at the site of absorption and also minimize any saliva wash-out effect which may lead to involuntary swallowing [6]. For these reasons, apart from the conventional tablet and liquid dosage forms available, newer dosage forms such as oral thin films and wafers are being developed. Oral transmucosal dosage forms must also allow for accurate and convenient dose measurement as the dose of all drugs varies with age and the weight of children. Other considerations include the ability of young patients to handle the particular dosage form, the physiological differences of the oral cavity between the adults and children, the palatability of the formulation and the cost effectiveness.

Buccal and sublingual routes, which are the two most common oral transmucosal routes of administration, are focused in this review. The oral transmucosal delivery systems have been reviewed recently in a number of publications without the specific consideration of the age of patients [3,4,7–10]. The development of buccal and sublingual formulations for systemic delivery targeting the pediatric population is the primary focus of this review.

2. Anatomy and physiology of the oral mucosal

Drug absorption through the oral mucosal surface is potentially effective because it is generally rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation or metabolism by gastric juice, gastrointestinal enzymes and first pass hepatic metabolism. The outer quarter to one-third of the oral mucosa is comprised of closely compacted, squamous stratified epithelial cells (Fig. 1). Beneath the epithelium are the basement membrane, lamina propria (an underlying supportive connective tissue layer) and submucosa which contains blood vessels and nerves, together with many taste sensory receptors dispersed among oral mucosa. The oral epithelia serve as a major penetration barrier to protect the underlying tissues against potential harmful materials or microorganisms in the oral environment, and also to prevent excessive loss of fluid from the underlying tissues to the exterior. Histologically, epithelia can be further developed into superficial keratinized and non-keratinized cells, which affect drug permeability, with the latter having a higher permeability [11]. This is due to the differences of lipid composition of the membrane coating granules in the keratinized and the non-keratinized cells, rather than the presence of keratin itself [12].

There are three major types of oral mucosa: the lining mucosa (60%), the masticatory mucosa (25%) and the specialized mucosa (15%). The lining mucosa contains the non-keratinized buccal and sublingual tissues in the oral cavity. The masticatory mucosa consists of keratinized hard palate (the upper surface of the mouth) and gingiva (gums), while specialized mucosa refers to the keratinized and some non-keratinized dorsal surface of the tongue. The highly keratinized palatal parts have poor drug permeability and are seldom pursued for drug delivery. Since lining mucosa is not subjected to masticatory activity, this non-keratinized mucosa is thinner than the other two mucosal types, and is more suitable for efficient drug absorption. Therefore, the buccal and sublingual routes are of primary interest for oral transmucosal drug delivery due to their higher overall permeability compared to the other forms of oral mucosa [7].

There are differences in permeability between the buccal and sublingual mucosa. Buccal tissues are the outer oral vestibule. With the buccal route of administration, drugs are usually placed on the inner cheek of

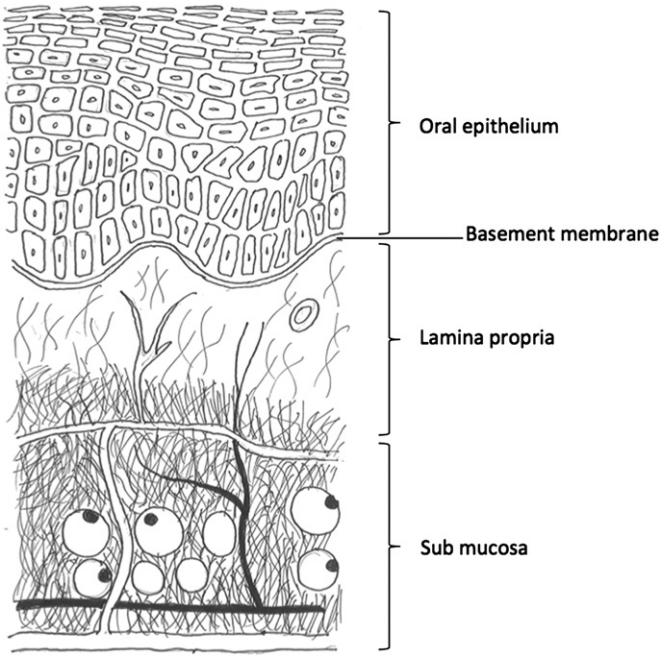

Fig. 1. The schematic diagram of the structure of oral mucosa.

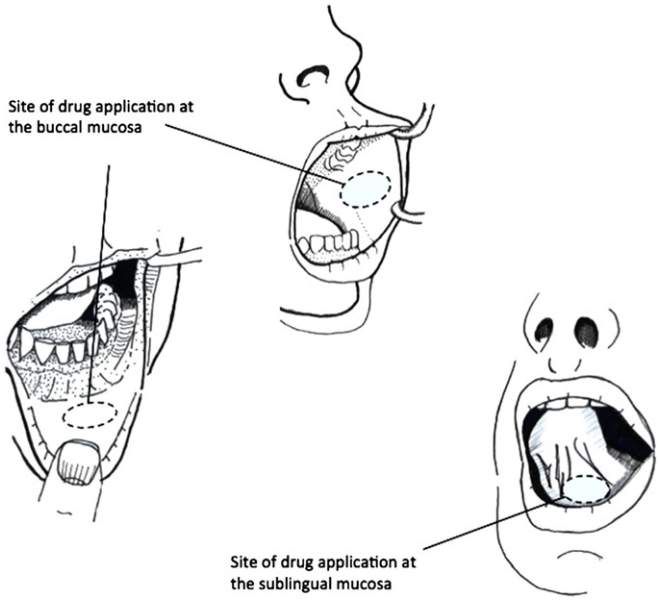

Fig. 2. Illustration of the common sites of drug application to buccal and sublingual mucosa.

the oral cavity, or in the buccal pouch between the cheek and gum. Sublingual tissues refer to the floor of the mouth and the drugs that are placed under the tongue are described as being administered via the sublingual route. Fig. 2 illustrates the common sites of drug application to buccal and sublingual mucosa. Based on the relative thickness and their different epithelial cell composition, the sublingual mucosa has higher drug permeability across the oral mucosa, plus its high vascularization makes it particularly suitable for rapid onset of systemic drug delivery, although the surface area of sublingual mucosa is smaller. Buccal tissues have a moderate permeability, and the buccal route is usually developed to achieve both local and systemic drug delivery with a relatively slow and predictable release. Table 1 summarizes the similarities and differences between the buccal and sublingual mucosa, and their absorption characteristics.

3. Physiological factors affecting drug absorption

3.1. Mucus

The surface of the oral mucosa is coated by a thin layer of mucus which presents one of the barriers to oral transmucosal delivery. Mucus is part of the saliva secreted by the salivary glands. The key component of mucus is mucin which belongs to a class of amphoteric macromolecular glycoprotein. Mucin only accounts for a small proportion (1–5%) of the entire mucus constitutes [8]. At normal oral mucosal pH, the mucus network is negatively charged due to the sialic acid and sulfate residues, and forms a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer [16]. Mucus exerts barrier properties by adhering tightly to the particles and by spreading as a thin film over the oral mucosal surfaces to trap further drug penetration. Conversely, mucus plays a critical role in the bioadhesion of mucoadhesive drug delivery systems [17]. The glycoprotein of mucus forms a complex with the functional group of either polymers or other drug excipients, thereby extends the site-specific drug retention time. In recent years, mucin has been widely adopted as the adherent substrate for different mucoadhesive materials [18]. The bioadhesion between mucins and the investigated polymers can provide important information on the behavior of designed polymer chain structures, particularly in terms of some desirable bioadhesive properties such as hydrogen bonding groups, ionic charges, chain flexibility, and surface energy properties favoring spreading, which promote potential bioadhesive polymers screening for oral transmucosal delivery formulation development [19]. The interaction between polymers and mucins to achieve mucoadhesive properties for oral transmucosal delivery will be discussed in more details in Section 5.2.

3.2. Saliva

Saliva is produced by three major glands: the parotid (40%), submandibular (40%), and sublingual glands (10%) as well as some minor salivary glands (10%) (Fig. 3). The acinus which is the small sac-like cavity in a gland is lined with acinar cells and secretes initial saliva. The initial saliva produced is an isotonic plasma-like solution with composition and ion concentrations similar to that of plasma. A branching duct system is lined with columnar epithelial cells, which serve to modify the initial saliva composition. Specifically, Na^+ and Cl^- are reabsorbed

Table 1
Comparison of properties between buccal and sublingual mucosa [8,11,13–15].

	Buccal mucosa	Sublingual mucosa
Drug location	Inner cheek, buccal pouch between the cheeks and gum	Under the tongue (the floor of the mouth)
Oral mucosal properties	• Non-keratinized; • 500–800 μm thick; • 40–50 cell layers; • An expanse of smooth muscle and relatively immobile mucosa; • Moderate vascularization	• Non-keratinized; • 100–200 μm thick; • 8–12 cell layers; • Lack of an expanse of smooth muscle or relatively immobile mucosa; • High vascularization
Permeability	• Absolute rate of water penetration: 579 ± 16 ($\times 10^{-7}$ cm/min) • Absolute rate of ovalbumin penetration: 178 ± 9 ($\times 10^{-7}$ cm/min)	• Absolute rate of water penetration: 973 ± 16 ($\times 10^{-7}$ cm/min) • Absolute rate of ovalbumin penetration: 426 ± 53 ($\times 10^{-7}$ cm/min)
Surface area	Adults: • 50.2 ± 2.9 (cm^2) Children (5 years old): • 30.1 ± 3.1 (cm^2)	Adults: • 26.5 ± 4.2 (cm^2) Children (5 years old): • 15.9 ± 3.8 (cm^2)
Drug delivery target	Local and systemic delivery	Systemic drug delivery
Application advantages	• Sustained drug delivery and chronic systemic therapy; • High tolerance to potential allergens, irreversible irritation or damage	• Rapid drug onset for acute treatment; • Drugs for short delivery period requirements
Potential problems	• Saliva wash-out effect; • Involuntary swallowing; • Retaining difficulty in buccal pouch; • Lower bioavailability: penetration enhancers, mucoadhesive polymers or enzyme inhibitors may be needed	• Saliva wash-out effect; • Involuntary swallowing; • Difficulty of keeping dosage in contact; • Device placement difficulty: lack of an expanse of smooth or immobile mucosa

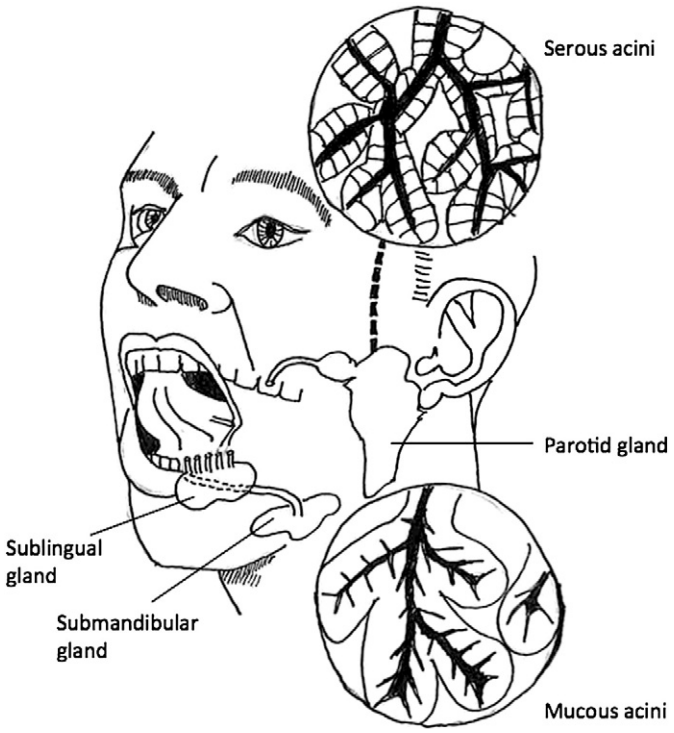

Fig. 3. Schematic diagram of the major salivary glands.

while K^+ and HCO_3^- are secreted by the ducts. These ducts are relatively impermeable to water and thus more solutes than water are reabsorbed by the ducts, resulting in the final diluted, hypotonic saliva [20]. Saliva is also rich in digestive enzymes such as α-amylase, lingual lipase, kallikrein, and various antimicrobial substances, such as immunoglobulins (IgA, IgM and IgG), lysozyme and other antimicrobial proteins and peptides [21,22], to act as the foremost portal of digestive system in human body.

The flow rate, composition as well as the pH of saliva may all influence the absorption of a drug in the oral cavity. The presence of saliva is important for drug absorption as it provides a relatively aqueous environment to facilitate drug release. However, excessive secretion and flow of saliva may lead to the premature swallowing of the dosage form and therefore a reduction in bioavailability and efficacy of the oral transmucosal drug; the so-called 'saliva wash-out effect'. In addition, the presence of digestive enzymes may also lead to degradation of peptide-based and protein-based drugs. The composition of saliva varies according to the salivary flow rate due to the variable duct contact time for reabsorption and secretion processes. At low flow rates, the saliva has the lowest osmolarity and *vice versa*. Saliva production is stimulated by both the parasympathetic and sympathetic nervous system, with the former activity being more important [20]. For this reason, saliva production can be increased by the presence of food in the mouth, smells, conditioned reflexes, and nausea due to parasympathetic nervous activation. Saliva production can also be decreased by sleeping, dehydration, fear and anticholinergic drug such as atropine due to the parasympathetic activity inhibition. All these factors may potentially affect and vary the oral transmucosal delivery efficiency.

3.3. Physiological difference between adults, children and infants

There are a limited number of studies that compare the physiological differences in the oral cavity between adults and children and more importantly, how these differences may affect the drug absorption through the oral mucosa. Here the noticeable difference in oral physiology of at different stages of life, and how these may affect the delivery of drug through the oral mucosa are discussed below.

The saliva flow rate does not remain constant over the life span of a human and similarly its composition also changes during early life, reaching a general adult composition with structural maturity of the glands [20]. Saliva is detected in infants soon after birth [23]. The flow rate appears to increase up to the age of around 5 to 6 years, after this stage the flow of saliva begins to decrease and the mean electrolyte content tends to increase [24]. The unstimulated salivary flow rate ranges from 0.22–0.82 ml/min in children to 0.33–1.42 ml/min in adults [23,25–27]. Watanabe and Dawes previously conducted a comparison of salivary flow rates and salivary film thickness between children (5 years old) and adults [14]. From their results, they concluded that the values of salivary flow rate and the volume of saliva produced in the mouth before and after swallowing in children were lower than those for adults. This was probably because the salivary glands of children under investigation had not been completely developed, and therefore had not reached the maximal secretory capacity. However, the average thickness of the saliva film was comparable to that observed in adults. Similar results reported that the rate of saliva secretion in the buccal mucosa was significantly lower in children (3 years old) than in young adults (20–25 years old) [28]. It is important to note that saliva flow rate is affected not only by age, but also by other external influences and nervous system activity. There is also a large variation between individuals. The effect of saliva flow rate on drug absorption cannot be determined solely by the age of patients. For example, children with Down syndrome, a genetic disorder caused by a trisomy of chromosome 21, have a lower saliva flow rate than children without Down syndrome [29,30].

In general, a high flow rate will increase the saliva wash-out effect, whereas a low flow rate may decrease the rate of drug dissolution and absorption. However, the optimal saliva flow rate for drug absorption has not been established as the absorption also depends on drug solubility, lipophilicity and other factors. Apart from the saliva flow rate, the concentration of various components in saliva, which is related to its flow rate, also varies at different age [31]. However there are inconsistencies about the relationship between saliva compositions and flow rate [27]. Reports of salivary flow rates and composition in healthy young children are limited, and to date, no previous studies have been carried out to investigate how these factors may affect oral transmucosal drug delivery in children, suggesting that further investigation is required.

pH is known to play a critical role in drug ionization and hence drug absorption. The oral mucosal pH of healthy children is around 6.6 [32,33], which is slightly lower but similar to that of an adult (pH 6.8) [34,35]. There are some differences between mean pH values at various sites of the oral cavity. For instance in adult, the pH of the floor of the mouth is around 6.5; the pH of the buccal mucosa is around 6.3; and the pH of the palate is around 7.3. Similar observations are made in children with the pH at the palate being higher than that of the mucosa. Other factors such as diet and saliva flow rate may also affect the pH of the oral mucosa. In general, as the saliva flow rate increases, the pH also increases [27]. The effect of pH on drug absorption will be discussed in Section 4.

The thickness of the oral mucosa has a direct effect on the rate of drug absorption. In adults, the thickness of buccal and sublingual mucosa is around 500–800 μm and 100–200 μm respectively (Table 1). Those available studies on the thickness of oral mucosa in infants and children, and their relative permeability are scarce. Interestingly, it has been reported that the thickness of masticatory oral mucosa is associated with age, with young adults (16–24 years) having thicker oral mucosa than the older age group (25–38 years) [36]. It is not known if the thickness of buccal and sublingual mucosa also follows a similar trend. However, a number of studies have pointed out that oral mucosa lesions are common in children and youths [37–39]. One of the most frequently reported lesion sites is the buccal mucosa caused by cheek biting (prevalence around 2–6% for children under 12 years old). This may have an impact on the drug absorption through the buccal route, but further investigation is needed to confirm this.

Table 2
The summary of the physicochemical properties of selected drugs that are investigated or used for buccal and/or sublingual delivery [41].

Drug (Salt)	Molecular weight (Da)	Log P[a]	Marketed buccal/ sublingual product
Buprenorphine (hydrochloride)	504.1	5.0	Y
Clonazepam	315.7	2.4	N
Diazepam	284.8	2.8	N
Fentanyl (citrate)	528.6	2.3	Y
Glyceryl trinitrate	227.1	1.6	Y
Lorazepam	321.2	2.4	N
Midazolam (hydrochloride)	362.2	4.3	Y
Morphine (sulfate)	758.8	−0.1	N
Nifedipine	346.3	2.2	N
Ondansetron (hydrochloride)	365.9	2.4	N
Oxycodone (hydrochloride)	405.9	0.7	N
Prochlorperazine (maleate)	606.1	4.9	Y
Zolpidem (tartrate)	764.9	3.9	Y

[a] Log P in octanol/water at pH 7.4.

In addition, infants and children are more susceptible to some specific oral infections than adults. For example, *Candida albicans* is a commensal organism of the oral cavity and responsible for oral candidiasis (Thrush). It is a common superficial fungal infection noted particularly more frequently in infants and young children than adults [40]. As the disease progresses, white non-adherent plaques appear on to the buccal mucosa and the palate is surrounded by erythematous areas. The occurrence of such oral infections in pediatric patients necessitates the cautious use of oral transmucosal drug since their application may provoke or irritate the already damaged oral cavity.

4. Drug selection

Low drug loading, including its molecular size and dose, limits the number of drug candidates that are suitable for development into oral transmucosal formulations. To improve the bioavailability following buccal or sublingual administration, several criteria of drug properties must be met in the first place. Table 2 summarizes the physicochemical properties of selected drugs that are investigated or used for buccal and/or sublingual delivery.

To identify suitable drug candidates for buccal or sublingual delivery, the difficulties associated with these routes of delivery must be understood. The outermost epithelial layers of the oral mucosa pose a major barrier to drug absorption. In general, both transcellular and paracellular pathways are involved, to a different extent according to the physicochemical properties of the drug, in transportation across the epithelial cells [4,42–46]. The transcellular pathway involves drug penetration through the cells until they reach the circulation. In order to facilitate passage across the lipid-rich epithelial cell membrane, drug candidates with high lipophilicity are favored. Typically, drugs that are developed for oral transmucosal delivery have a log P value (octanol/water) above 2.0, which means that the drug(s) are at least 100 times more readily soluble in octanol than in water. The drug should also have a fairly good water solubility to allow drug diffusion across the hydrophilic cytoplasm of the cells. This poses a problem for highly lipophilic drug which tends to have poor water solubility. Selection of the salt form of a drug with good water solubility could be considered. For example, fentanyl in its free base form (only sparingly soluble in water) is used in a transdermal formulation because high lipophilicity is important in order to cross the lipidic stratum corneum layer in the skin [47,48], whereas the salt form, fentanyl citrate (water solubility = 2.5 g/100 ml), is used in the oromucosal formulation to improve the solubility [49,50]. In addition, drug molecules are more effectively absorbed when they are in their unionized form and are able to partition into the lipid-rich biological membranes. For this reason, the pKa value of a drug has become important as it determines the degree of ionization of a drug at different pH. Ideally, drugs should be predominately in their unionized forms at the site of the oral mucosal, hence allowing for better absorption.

Apart from the transcellular pathway route of absorption, the paracellular pathway exists in which drug permeation occurs between cells. This is an important route for the passage of hydrophilic drugs. Due to the presence of tight junctions between the adjacent cells, permeation enhancers may be required to induce a temporary enhancement of mucosal permeability [51]. Depending on their physicochemical properties, some drugs may permeate through the mucosal via both transcellular and paracellular pathways. Passive diffusion is the mechanism of transport in both routes of permeation and consequently, the smaller the molecular size of a drug, the easier the transportation across the epithelial cell layers will be. A good drug candidate should have a molecular weight not higher than 800 Da. In addition, due to the limited volume and surface area for absorption in buccal or sublingual area, drug loading is relatively small. Only a few milligrams of drug can cross the oral mucosa [8]. Therefore the drug candidate must have a relatively high potency and must not cause any local irritation at the oral mucosal. The ideal physicochemical properties of a drug candidate are summarized in Table 3. Examples of drug that fulfill most of these criteria include buprenorphine, fentanyl and midazolam, which have been successfully developed into buccal or sublingual formulations in the market.

5. Formulation consideration and strategies

Pediatric patients as a group include neonates, infants, children and adolescents and each of these subgroups encompasses a variety of ages, body size and weights. With changes in the age of patients, there are also changes in the ability to handle different dosage forms. For example, younger patients are more likely to experience dysphagia, which is less common in the adult population. In general, small volume liquid medicines are suitable for most ages whereas solid dosage forms are more convenient to the lifestyle of adolescents. Unlike adults, palatability remains one of the major determinants of oral mucosal contact time and adherence in children [52,53]. This is of particular importance due to the lack of cooperation of children, their difficulty in coordination, and the risk of choking and aspiration. Pediatric patients are still experiencing physiological development, and consequently the dose of a drug, which is frequently determined by a patient's body weight, may result in as much as a fifty-fold difference in various age groups [2]. The accuracy of dosing is therefore a real challenge, since oral mucosal dosage forms may be swallowed or spat out prior to sufficient absorption having taken place. Mucoadhesive polymers and permeation enhancers are commonly employed in the oral transmucosal delivery system to improve the bioavailability [6,54–56].

5.1. Choices of excipients

Since the organs of young patients and their respective metabolic functions are still developing, the choices and also the quantities of pharmaceutical excipients used in formulations have to be carefully considered. This is primarily due to the fact that these chosen excipients may remain in the body for a prolong period of time due to reduced metabolic capacity and/or reduced renal elimination, thus exposing children and infants to a number of potentially serious toxicities

Table 3
The summary of ideal physicochemical properties of drug candidates for buccal or sublingual formulation development.

Parameters	Ideal properties
High potency	Single dose <10 mg
High lipophilicity	Log P (octanol/water) >2.0
Fairly good water solubility	Select drug salts with good solubility if necessary
Acid/base properties	Unionized form at mucosal
Small molecular size	Smaller the better, less than 800 Da

[57,58]. Excipients associated with an elevated risk of toxicity in pediatric patients include benzyl alcohol, ethanol and propylene glycol [59–62], which are commonly used as co-solvents in many pharmaceutical preparations. Some excipients may also readily enter the brain as the blood–brain barrier is not fully developed in children and is found to be more permeable than in adults. One of the examples is the use of benzyl alcohol. The notorious case of 'gasping syndrome' associated with the use of benzyl alcohol was first described in 1981, causing severe neurotoxic effects and brain damage to neonates [61,63]. Other excipients, such as parabens, benzalkonium chloride, dextran and sodium bisulfite, may activate the immune system of the developing children and induce allergies or anaphylactic reactions which may be severe and even live-threatening [58,64].

Formulations with an unpleasant taste may easily lead to the voluntary removal of dosage form from the oral cavity instead of retention at the site of delivery, therefore limiting the absorption of drugs via the oral mucosa. Consequently both sweetening and flavoring agents should be considered especially in pediatric formulations. Natural sugars such as sucrose, fructose and glucose are commonly used in pediatric pharmaceutical formulations. However since these formulations are intended to remain in the oral cavity for an extended period of time, they may create a low oral pH environment and increase the risk of tooth decay in children [65,66]. Oral hygiene maintenance should be recommended after the use of sugared medication. The use of sugar containing formulae should also be strictly limited or totally avoided in children and adolescents with type 1 diabetes mellitus. Artificial sweeteners such as saccharin, aspartame, acesulfame-K and sucralose have been used to partly substitute natural sugar in pharmaceutical preparations. These artificial sweeteners are in the order of magnitude of one hundred to a thousand times sweeter than sucrose. However, there has been concern regarding the clinical safety of artificial sweetener for children [57]. In addition, sugars and sweeteners are known to have a saliva stimulating effect, which may affect the drug absorption rate. For instance, an increase in saliva volume may improve tablet disintegration and allow for rapid drug release, but this may also promote saliva wash-out and ultimately the swallowing of the formulation. Apart from sweetening agents, flavoring agents are also commonly included in pediatric formulations in order to impart an acceptable taste. A number of allergic reactions have been possibly associated with sweetening and flavoring agents [67]. Some children may suffer from rare disorders such as phenylketonuria, fructose or lactose intolerance. In such cases, excipients such as aspartame, fructose, sucrose and sorbitol should be avoided [58]. The safety of the use of all types of excipients in pediatric formulation must not be overlooked.

5.2. Mucoadhesive polymers

Mucoadhesive polymers are essential in maintaining a prolonged period of contact between the formulation and the oral mucosal. Apart from the mucoadhesive properties, these polymers must also be biocompatible and non-toxic. Early generation mucoadhesive polymers such as linear poly(ethylene glycol) provided a non-specific interaction with the mucosal surface, usually through the hydrogen bonding or electrostatic interaction. The second generation of mucoadhesive polymers provided a more specific interaction platform with the mucosal surface. Poly(acrylic acid)derivatives, polymethacrylate derivatives and cellulose ester derivatives are commonly used mucoadhesive agents [68–70]. Their mucoadhesive properties are attributed to strong hydrogen bond interactions with mucins [71]. Chitosan is one of the most widely investigated polymers for this purpose in recent years. It is extensively used as food supplement but has yet to be approved by the FDA in the application of drug delivery. Chitosan is a natural polysaccharide and is well known for its biodegradable and non-toxic properties. Its cationic nature allows it to bind with the negative charged sialic acid moieties of the mucus [72]. To further improve the mucoadhesive properties, thiolated polymers have been developed to allow the free thiol group of the polymers to form disulfide bonds with glycoproteins of the mucus components as well as the mucosal cell surfaces [73–76]. This covalent interaction provides a stronger adhesion to the oral mucosal as it is less affected by the changes in ionic or pH of the environment [77]. However, the use of chitosan in terms of efficacy and safety has not been investigated in the pediatric population. Target specific mucoadhesive materials have been investigated recently. Specific proteins or glycoproteins such as lectins, which are able to bind to certain sugars on the cell membrane, can improve adhesion and hence extend residence time in mucosal surface [78,79]. However the effect of repeated exposure of children to lectins is not clear.

5.3. Permeation enhancers

Passive diffusion via the paracellular and transcellular pathways is both involved in the transportation of drug across the oral mucosa. Drugs that are suitable for absorption through passive diffusion are limited by their physiochemical properties as discussed previously. The relatively short retention time at the site of absorption, the presence of a mucus layer and the small surface area available for absorption (compared to the intestine) further decrease their bioavailability. Strategies have been developed to enhance the transportation of molecules across the epithelial cells, by using a 'permeation enhancer' or 'penetration enhancer'. These agents improve mucosal absorption by different mechanisms. For example, fatty acids (e.g. oleic acid) can alter cell membrane structure by inducing lipid fluidization and phase separation within the membrane [80]. Cyclodextrin acts as permeation enhancers by increasing drug availability at the surface of the biological barrier [81]. Surfactants (e.g. sodium dodecyl sulfate) cause perturbation of intracellular lipids and protein domain integrity [82]. Bile salts (e.g. sodium deoxycholate) act by the extraction of membrane proteins or lipids and consequent membrane fluidization, thus creating aqueous channels [83]. Enzyme inhibitors (e.g. aprotinin) have also been documented to improve drug permeation across the buccal mucosa [84]. As discussed earlier, chitosan has been extensively investigated for transmucosal delivery. Apart from its mucoadhesive property, it has been explored for its potential role in enhancing mucosa permeation by the modulation of tight junction complexes, and thereby increasing paracellular drug transport including solutions and powders [85–87]. One of the fundamental criteria required of permeation enhancers in the formulation of buccal or sublingual systems is that they are non-toxic at their effective concentration. The imperative is that any adverse effects caused by these agents must be transient and reversible, and that they must not cause any permanent damage to the oral mucosa.

5.4. Dosage forms

Development of a suitable dosage form for pediatric patients is always a challenge [88]. Conventional oral transmucosal dosage forms include tablets, liquids and chewing gums. Chewing gum may not be a suitable dosage form for pediatric patients because of the requirement of a chewing action and the ability not to swallow the chewing gum mass, as well as specific techniques (e.g. 'the park and chew' cycle), which are often difficult or even dangerous for younger patients. Consequently, it could be difficult to control the dose and the rate of drug being released from the formulation. Chewing gum formulations which are reviewed elsewhere [89] are not discussed in detail here. Tablets and lozenges are solid dosage forms that require less coordination than chewing gum formulations, but again are still not ideal due to a similar risk of choking and aspiration for in younger patients. Also the use of mucosal adhesive materials in tablet formulations may provoke oral discomfort particularly when the removal of this type of dosage form from the oral mucosa is required. In addition these types of dosage form may possibly be swallowed and adhere to the wall of esophagus. Young children may also find it difficult to retain the formulation against the oral mucosal for a sufficient period in order to allow

complete drug release and absorption. Therefore solid dosage forms should only be considered for older children and adolescents. Liquid forms including solutions and suspensions are considered to be more appropriate for young patients. The major disadvantages of liquid dosage forms are the relatively short contact time with the mucosal surface and that they are easily diluted by saliva, resulting in the swallowing reflex and thus removal of the medication from the site of absorption in the oral cavity. In addition, to ensure the solubility and/or stability of the liquid formulation, excipients need to be included. The level and choice of excipients used must be carefully monitored. Other newer formulations such as oral thin-films and wafers are being investigated to improve the contact with the oral mucosa and overall bioavailability. Examples of oral transmucosal dosage forms that are approved for pediatric use are listed in Table 4.

5.4.1. Tablets and lozenges

The solid dosage form remains one of the most popular methods of drug administration. The unit dosage system can also ensure accurate dose administration which is particularly important in pediatric patients. Buccal tablets are placed into contact with the buccal mucosa (e.g. between lip and gums) and are left to dissolve, whereas sublingual tablets are placed under the tongue for absorption. Lozenges sometimes come with applicators which may ease the process of drug administration. They are usually placed between cheeks and gums where the patients can actively suck on the medicine. All these administration methods remove the necessity for the patient to swallow the entire dosage form. Patients should also be advised not to chew the tablets or lozenges. Depending on the formulation, the tablet generally disintegrates and dissolves rapidly, usually within 15 to 30 min, to allow immediate drug release, or adheres to the mucosa to allow prolonged drug release. In the case of disintegrating tablets, rapid disintegration can be achieved by incorporating superdisintegrants such as polyplasdone, croscarmellose sodium and sodium starch glycolate into the formulation [90,91]. At the same time, these tablets must be sufficiently robust to withstand the physical forces experienced during handling and transportation. Lozenges usually contain a dissolvable sugar-based matrix. The dissolution and disintegration of lozenges are usually controlled by the patient themselves, e.g. by how vigorously and frequently they suck on the unit. A sucking action stimulates saliva production, which may lead to uncontrolled swallowing. Lozenges are formulated with the consideration that they may be absorbed via the gastrointestinal tract.

Table 4
Examples of oral transmucosal formulations for pediatric use (below 18 years old).

Active ingredients	Indications	Dosage form	Brands	Age
Buprenorphine	Pain management	Sublingual tablet	Temgesic®	>6 years
Buprenorphine/naloxone	Opioid dependence	Sublingual film	Suboxone®	>16 years
		Sublingual tablet	Suboxone®	>16 years
Fentanyl	Breakthrough pain management	Lozenges	Actiq®	>16 years
Grass pollens	Grass pollen allergic rhinitis	Sublingual tablet	Oralair®, Grazax®	>5 years
Midazolam	Acute seizures	Buccal solution	Buccolam®	>3 months
Nicotine	Smoking cessation	Sublingual tablet	Nicorette® microtab	>12 years
		Chewing gum	Nicorette®, NiQuitin®, Nicotinell®	>12 years
		Lozenges	NiQuitin®, Nicotinell®	>12 years
Prochlorperazine	Vertigo, nausea, vomiting	Buccal tablet	Buccastem®	>12 years

Saliva volume is an important factor that affects the rate of drug absorption as mentioned previously. After a tablet is placed at the intended site of absorption inside the oral cavity, saliva quickly penetrates into the tablet body causing rapid disintegration. Reduced saliva production may slow down the rate of disintegration and hence drug absorption. On the contrary, increased saliva production may stimulate swallowing and thus a decrease bioavailability, with passage to the stomach. With those tablets that are formulated to provide a sustained/prolonged release, they generally consist of a mucoadhesive polymer matrix which can be designed to control the rate of polymer degradation (leading to bulk erosion or surface erosion of tablet) or drug diffusion, and/or a combination of both actions, and hence control the rate of drug release [54]. The development of buccal tablets that readily adhere to the oral mucosal without causing patient discomfort remains a key challenge. In addition to the potential of mouth discomfort, taste is a critical factor in achieving patient acceptability. Sweetening and flavoring agents should be used if necessary to mask the taste of the drug and make it palatable. Buccal and sublingual tablets, as well as lozenges have been used for adolescent and older children (usually above 12 years of age) as they are mature enough to follow the administration instruction without a high risk of choking and aspiration. However for long-term treatment, younger children may be taught to take tablets.

5.4.2. Oral films and wafers

Oral films, also referred to as oral strips or patches, are relatively new dosage forms that provide safe and convenient unit dosage systems suitable for the pediatric population [3]. These stamp-like dosage forms are usually 1–3 cm^2 in size, but possibly could be tailored to a larger size to accommodate a high dose of drug, with an ideal thickness of less than 1 mm to allow ease of application in the mucosal area [92]. Compared to conventional oral tablet formulations, they are ultra-thin, flexible and tend to be less obtrusive, and therefore cause less oral discomfort, better adapted to the mucosal surface and more acceptable to younger patients. These films also dissolve more quickly than the conventional buccal or sublingual tablets. Compared to liquid formulations, they offer a precise dose administration and ease of handling. However, the overall delicate characteristic of these dosage forms makes them susceptible to over-hydration which readily results in the loss of their adhesive properties. In addition their fine structure results in a further reduced capacity for total drug dose.

The ideal oral film should exhibit adequate flexibility, elasticity, softness, good mucoadhesive properties and resistance to breakage due to stress from oral activity [93]. The key component of an oral film formulation is the film-forming polymer that is essential for rapid dissolution in the buccal cavity to ensure immediate drug delivery without causing the loss of mucoadhesion, therefore a balance between dissolution and adhesion must be struck. In addition, the polymer properties that allow for rapid dissolution must be balanced with an adequately robust structure to avoid any damage during handling or transportation. In addition, the polymer employed must be non-toxic and non-irritant to oral mucosa. Polymers that are commonly used in the development of oral films include hydroxypropylmethyl cellulose (HPMC), pullulan, modified starch, gelatin, sodium alginate, carboxymethylcellulose, carrageenan and chitosan [92,94–97]. These materials all have film-forming capacity and are commonly used in pharmaceutical formulations such as capsule shells, tablet coating agents, suspending agents and thickening agents, and are known to be safe for human use. They are frequently used in combination in order to achieve the required strength, flexibility, hydrophilicity, and solubility properties. The film-forming polymer is the major component of the film and contributes at least 45% of the total weight of the dry film [94].

To prepare the polymeric film, the solvent casting method is commonly employed [98–103]. In this process, the polymers are dissolved in a suitable solvent in which the drug is also dissolved or dispersed. Plasticizers are usually incorporated into the mixture to enhance the flexibility and reduce the brittleness of the film by reducing the glass

transition temperature of the polymer. Common plasticizers include glycerol, propylene glycol, low molecular weight polyethylene glycol (PEG) and phthalate derivatives. Subsequently the mixture is cast onto a substrate surface and the solvent is allowed to evaporate, leading to the formation of a drug-containing polymeric film. Alternatively, hot-melt extrusion is another method to prepare an oral film [104–107]. It has the advantage of avoiding the use of organic solvent but is not suitable for thermo-labile compounds [108]. Drugs and excipients are mixed in a dry state and subjected to heating. Subsequently they are extruded out in a molten state, cooled and cut to the desired size. Oral films that are designed for prolonged drug release, mucoadhesive polymers are employed to extend the residence time of the films in the oral cavity by strengthening the adhesion to the buccal mucosa.

Oral films are usually applied to the buccal or sublingual mucosa, although few are designed for application to the gingival mucosa. Films with a dissolvable matrix are designed to either release drug immediately to the oral cavity, or to contain a mucoadhesive layer which will prolong site retention time. Films with non-dissolvable backing are designed to protect the formulation from saliva and prolong drug release to over 10 h. However these films require the backing to be removed after drug administration and are therefore less suitable for children to use. In addition, patients should also be advised not to cut the formulation, as this may affect the rate of drug release.

Similar to oral films are oral lyophilized wafers, which are thin, flat disk-like dosage form that are currently undergoing investigation for drug absorption through the oral mucosal [109–114]. Lyophilized wafers have also been used in wound healing drug delivery [115,116]. This relatively new type of dosage form is usually prepared by lyophilizing aqueous gels of mucoadhesive polymer such as chitosan, carrageenan and sodium carboxymethylcellulose, incorporating plasticizers and cryoprotectant. Compared to oral films, the porous structures of lyophilized wafers generally allow quicker rate of drug release [110], making the wafer formulations more suitable for rapid delivery.

Oral films containing fentanyl citrate (Onsolis®) and buprenorphine/naloxone (Suboxone®) are available in the market for adult use. Products that are suitable for children use are mainly vitamin strips to avoid swallowing. Since both oral films and lyophilized wafers have a huge clinical potential for pediatric patients with the possibility of unit-dose system and ease of administration, especially suitable for rapid onset of action. Further investigation is required in this area.

5.4.3. Liquids

Aqueous solutions and suspensions are also used for oral mucosal delivery. Although liquids are preferred for younger patients due to safety reasons (i.e., minimize the risk of choking associated with solid dosage form, or injury associated with the use of needles for injection), the biggest limitation of this type of formulation is that they are not easily retained in the oral cavity and may result in being swallowed before transmucosal absorption can take place. As a consequence of this, the amount of drugs being delivered cannot be controlled precisely. Mucoadhesive polymers such as chitosan and sodium alginate have been investigated to improve drug absorption of liquid formulations by coating the mucosa [117]. In addition, these polymers can also increase the viscosity of liquid formulations which allows for an extended period of contact at the site of absorption. Again, taste may affect the retention time of liquids in the mouth of young patients. Sweetening and flavoring agents may be considered in these formulations when necessary. Recently iontophoretic techniques have been investigated to improve drug delivery in liquid forms across the buccal mucosa *in vivo* [118,119]. More studies are required to determine whether this method is effective and safe for pediatric use. The oral aerosol spray is another suitable alternative to deliver drug onto the mucosal surface [3]. Accurate dose measurement may be a problem which could be tackled with metered dose spray device.

Since the surface area of the oral mucosa and the size of the oral cavity vary with age, thus the volume of medication that may be administered comfortably for suitable drug absorption across the oral mucosa will also depend on a patient's age. In general, it is considered that children under 6 years old should not receive more than 5 ml in volume of a liquid, and children above 6 years old should not receive a volume greater than 10 ml. It is also suggested that less palatable drugs be administered in smaller volumes than normal in children [3]. Accurate dose measurement is potentially difficult when the volume being measured is very small. This problem could be overcome by packaging the liquid formulations in pre-filled oral syringes as a unit dose. For example, Buccolam® (midazolam hydrochloride), a marketed buccal solution for the treatment of acute seizures in children and infants above three months old, is packaged in pre-filled oral syringes [120]. However, this would obviously increase the cost of manufacture.

6. Clinical benefits

Since the buccal or sublingual formulations are associated with higher cost of manufacture, there must be a clear clinical benefit to make such a development worthwhile. For systemic drug delivery, the oral route of administration is generally the preferred route of administration due to its non-invasive nature and low production costs of the respective medication. When the oral route is not suitable, a safe alternative route must be considered. One of the key advantages of buccal or sublingual route is that it avoids first pass metabolism. This is particularly useful when formulating drugs with poor oral bioavailability due to extensive hepatic metabolism, but this reason alone is not sufficient to justify for oral transmucosal drug development. Although many drugs have been evaluated with oral transmucosal delivery, only a few are currently commercially available. Apart from the necessary physicochemical properties of the drug, it must also be accompanied with a clear clinical benefit to make such development worthwhile. Below are a few examples of conditions where oral transmucosal route has potential clinical benefits for pediatric patients, given that the oral route is not appropriate.

6.1. Emergency medicine

When rapid onset of action is required in an emergency situation, the parenteral route is often considered as the route of choice. Although high bioavailability is guaranteed, parenteral administration requires sterile equipment and special skills. Painful injection also means that patients, especially young children, may not be co-operative. There may be also difficulties in accessing the intravenous route in young patients. This becomes problematic when healthcare professionals are unavailable outside the hospital settings during the emergency situation. Administration of a drug via the oral mucosal offers an alternative way of administration that is easy, pain-free and non-invasive.

Buccal delivery and sublingual delivery of benzodiazepines have been explored and used for the treatment of acute seizures in children [121]. Status epilepticus is a life threatening condition and is the most common childhood neurological emergency experienced in developed countries. Immediate diagnosis and rapid treatment are the keys to prevent neurologic damage in a seizure episode. Although intravenous administration of antiepileptic drugs is the most efficient way to control seizures during an emergency situation, it needs the assistance of well-trained healthcare professionals and venous access in such emergencies is particularly difficult, especially in children. Consequently an easy administered medication would be highly desirable for treating seizures in younger patients particularly in the community setting.

The most successful case of oral transmucosal formulation of antiepileptic drugs for children is perhaps the buccal midazolam. Midazolam undergoes extensive first-pass hepatic metabolism. Due to its small molecular weight and high lipophilicity at physiological pH, rapid absorption across the buccal mucous membrane can be readily achieved, making it a perfect candidate for buccal formulation development. Following the buccal administration of midazolam, a rapid onset

of action of less than 10 min can be achieved with a short duration of effect [122]. Buccolam®, a buccal solution of midazolam hydrochloride, became the first medicine granted by the new European Union Paediatric-Use Marketing Authorization (PUMA), which was licensed in 2011 in Europe for the treatment of status epilepticus and prolonged seizures in children and infants above the age of 3 months old. Prior to this, rectal diazepam was the only licensed treatment for this condition and consequently many studies have been conducted to compare between buccal midazolam and rectal diazepam in pediatric patients. The results from various clinical studies showed that buccal midazolam was either equally effective as or superior to rectal diazepam [123]. It is not difficult to understand that buccal midazolam is also a more acceptable choice to the patients' family or carer. The most commonly stated reasons include personal dignity; fewer ethical considerations, particularly in pediatric patients; ease of administration for wheelchair users; and a quicker response than rectal diazepam [124]. In terms of safety, the frequency and the severity of adverse drug reactions reported for buccal midazolam were similar to that of the rectal diazepam comparative group, as well as to those reported with other benzodiazepines. Apart from midazolam, several other benzodiazepines are also being investigated for oral transmucosal delivery. Sublingual lorazepam has been shown to be more rapidly absorbed than with oral ingestion [125], however buccal lorazepam was found to be less effective in stopping seizures than the intravenous route in children with status epilepticus [126]. A diazepam oral patch has also been developed and an animal study demonstrated that although rapid absorption was achieved to reach therapeutically effective plasma concentration, the maintenance of the plasma level was less than satisfactory [127].

Apart from seizures, hypoglycemia is another medical emergency often experienced in infants and children and is most common in the premature newborn. Other causes of pediatric hypoglycemia include poor diabetes management, malnutrition due to lack of food and protein intake, especially in developing countries where access to medical care is difficult. The standard treatment of hypoglycemia includes oral or intravenous infusion of glucose solution. Administration of glucose through the sublingual mucosa offers a potentially effective and cheaper alternative. It was found that the bioavailability of sublingual glucose (approximately 84%) is higher than oral glucose (approximately 38%), and comparable to the intravenous route of administration [128]. Sublingual glucose has been demonstrated to have an onset of action similar to that seen with intravenous administration in the treatment of hypoglycemia in children [128]. Similarly, the sublingual administration of glucose was found to be effective in those children with moderate hypoglycemia caused by malaria infection [129,130]. This simple and promising method to control hypoglycemia could be further explored in emergency treatment regimens, especially in those developing countries where medical facilities are not well equipped.

6.2. Opioid analgesics

In chronic pain management where repeated dosing of analgesics is necessary, a route of administration that produces less patient discomfort has become increasingly important to enhance compliance especially in younger patients. Breakthrough pain is a type of pain that is frequently experienced in cancer patients including children. A breakthrough pain episode is a period of time when blood levels of regularly administered analgesics are below the level required to induce analgesia, resulting in sudden intense episodes of pain in patients. A rapid onset and short duration of action is pivotal in the treatment of breakthrough pain. In children, a breakthrough pain episode typically lasts seconds to minutes. It is difficult to manage breakthrough pain rapidly via the oral route as drug absorption and consequently adequate plasma levels of analgesics are relatively slow to achieve.

Opioid analgesics such as fentanyl and buprenorphine have relatively poor oral bioavailability and are frequently the subject of drug delivery models where an alternative route of administration such as oral-transmucosal, transdermal and intranasal delivery is necessary. Compared to other non-parenteral routes of administration, oral transmucosal delivery appears to have fewer limitations and the absorption via this route is on the whole more predictable. The selection of suitable therapeutic agents for transdermal delivery is very stringent due to the physiology of the stratum corneum layer which is a significant barrier to the absorption of most drug molecules. The permeability of the skin may vary significantly with age and in addition, the long-term application of transdermal patches may also cause local skin irritation. Another common problem with drug absorption across the nasal mucosal is that some drugs may adversely provoke nasal congestion, increased nasal mucosa sensitivity, mucus production, post-nasal drip and in extreme cases upper respiratory tract infections. As a consequence of addressing these defined problems, oral-transmucosal drug delivery is an attractive administration route for opioids for pain management in pediatric patients.

Fentanyl is a highly potent opioid (100–300 fold more potent than morphine), which is frequently used in pain management in cancer patients. Due to high first-pass metabolism, fentanyl is not suitable for oral administration. Its high lipophilicity (Log $P = 2.3$) makes it a suitable candidate for oral transmucosal delivery. Oral transmucosal fentanyl provides a painless method of opioid administration and is acceptable to most children. Buccal lozenges (Actiq®, Fentanyl Oralet®) of fentanyl are approved for the management of breakthrough pain in cancer patients above 16 years of age, whereas buccal tablets (Effentora®, Fentora®) and sublingual tablets (Abstral®) are approved for patients above 18 years of age only. The major problem encountered with these preparations was primarily the lack of cooperation of younger children. A study conducted by Wheeler et al. [131] investigated the uptake pharmacokinetic of buccal fentanyl in children aged between 3 and 10 years old. The result showed that the bioavailability and peak plasma concentrations of buccal fentanyl were low, suggesting that many children swallowed a large fraction of the dose. The risk of choking and aspiration of the oral dosage form is also problematic.

Buprenorphine is a partial μ-opioid receptor agonist, and κ- and δ-receptor antagonist. It undergoes extensive first-pass metabolism and its oral bioavailability is only 10–16%. It is 30–50 times more potent than morphine. Buprenorphine has an established safety profile in adults. Compared to other opioids, it has a ceiling effect for respiratory depression [132,133] and an analgesic effect with a lower risk for fatal intoxications [134]. Buprenorphine is a suitable candidate for sublingual delivery due to its high lipophilicity and potency. Following sublingual administration, the bioavailability is increased to around 50% [135]. Sublingual buprenorphine has been routinely used in the treatment of adult opiate addiction and moderate to severe pain management. In recent years, the use of buprenorphine in pediatric patients has increased. The pediatric clinical indications of buprenorphine include the relief of post-operative pain and cancer pain, premedication and abstinence syndrome. Buprenorphine overdoses are generally well tolerated and healthy children who have ingested high doses have experienced minimal toxicity [136,137] but this may in part be attributable to high first pass clearance after oral administration. However there are still concerns regarding the safety of use of buprenorphine in children [138].

In 1985, a small retrospective study was carried out to investigate the use of sublingual buprenorphine for cancer pain management in children [139]. It was found that 12 out of 13 patients given sublingual buprenorphine experienced complete pain-free periods with only minimal adverse effects. No patient required drug discontinuation. More recently, Kraft et al. [140] studied the feasibility and safety of sublingual buprenorphine in the treatment of neonatal abstinence syndrome (NAS) in neonates. NAS is a complex condition which is defined as the signs and symptoms in the postnatal period associated with the sudden withdrawal of maternally transferred opioids and other therapeutic agents, including antihistamines and tricyclic antidepressants. Buprenorphine solution was administered to patients under the tongue followed by insertion of a pacifier to reduce

swallowing. Although the sample size was small (13 patients in total), the results suggested that buprenorphine administered via the sublingual route was feasible and was largely effective in controlling NAS and may represent a novel treatment for this condition. Currently, sublingual buprenorphine (Temgesic®) is approved for children above the age of 6 years. Sublingual buprenorphine/naloxone formulations (Suboxone®) are also approved for adolescent above 16 years old for the treatment of opioid dependence.

6.3. Mucosal vaccination

Immunization is a disease prevention measure that most often takes place within the early stages of life. Infants and children are frequently immunized for protection against various infectious diseases. Currently, the parenteral route is the most common route of vaccine delivery. In recent years, the mucosal surface, including the oral mucosa, has received much attention as the potential delivery site for vaccines [141,142]. Apart from its non-invasive nature, which is highly desirable considering that young patients often received multiple vaccines including boosters, the major advantage of mucosal vaccination over parenteral vaccination is that it can induce both mucosal and systemic immune responses, resulting in double layers of host protection. Local mucosal immunization leads to antigen-specific IgA production at distant mucosal sites, including the small intestine, respiratory and genital tissues, which means that oral mucosal vaccination has the potential to offer protection against intestinal, respiratory and genital infections.

Animal studies showed that sublingual administration of inactivated influenza virus can induce the production of specific IgA antibodies. In addition, the sublingual vaccination did not elicit IgE antibodies, suggesting that this route of vaccination could avoid the danger of anaphylactic shock and/or allergic reactions provoked IgE antibodies. In the same study, it was found that mice that were sublingually vaccinated with inactivated influenza virus plus mucosal adjuvant showed complete clearance of the virus [143]. Apart from respiratory infections, sublingual vaccination also effectively protected mice against genital human papillomavirus (HPV) infection [144]. Mice that were sublingually immunized with HPV-like particles showed complete protection against HPV infection. However controlled clinical trials will be necessary to determine the safety and efficacy of this administration route of vaccine originally formulated for delivery by other routes.

6.4. Sublingual immunotherapy (SLIT)

Allergen-specific immunotherapy is a strategy used to manage IgE-mediated allergies such as insect allergy, allergic rhinitis and allergy provoked asthma, by inducing immunogenic tolerance through repeated administration of specific allergens. It is the only treatment for allergies that has a disease modifying effect [145]. This approach is used in both adults and children, although the scientific evidence for the effective use in children is not as strong as that for adults [146]. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are currently used in clinical practice and these two routes of administration are always compared in clinical studies. In general, SLIT is preferred rather than SCIT especially in children due to its non-invasive nature and the ease of administration, especially where the chronic repeated administration of these agents is required.

Although many studies have been performed to evaluate the efficacy and safety of SLIT, the exact mechanism is still not entirely clear. There is a difference in the mechanism between SCIT and SLIT and it appears that the contact allergen with the oral mucosa is an important factor in SLIT in order to induce the systemic response as well as the local immune reaction which requires allergen uptake by specific dendritic cells in the oral cavity. In the early studies, the efficacy of SLIT in children was somewhat controversial [147–150] primarily due to poor study design which affected the reliability of these initial studies [145]. More recently, studies have shown that SLIT can improve symptoms and reduce the number of episodes over three years of treatment, indicating disease modification and associated long term benefits [151,152]. In addition this technique has demonstrated that it is effective in those children where therapy was performed prior to – and concomitantly with the – allergy season i.e. spring and summer with pollen for a one-year period [153,154].

In terms of safety, SLIT is believed to be a safer option, as it is better tolerated than SCIT and can avoid serious adverse effects such as the risk of fatal anaphylaxis, which is associated with the subcutaneous route. However SLIT and SCIT have similar high rate of mild local unwanted effects. Commonly reported adverse effects include oral itching, swelling, irritation and mild gastrointestinal effects [155]. However serious adverse effects are rare and no fatalities have been reported in children [145].

SLIT is available as sublingual tablets and sublingual drops. The tablets or drops are held under tongue for 1–2 min and then swallowed. To date, two SLIT products are approved on the European market. Oralair® is a sublingual tablet containing a mixture of five grass pollens [156]. It is indicated for the management of grass pollen allergic rhinitis with or without conjunctivitis. Grazax® is another sublingual tablet formulation containing only one grass pollen and is indicated for treatment of grass pollen allergic rhinitis and conjunctivitis [157]. Both products are suitable for use in adults and children above 5 years of age. However, no form of SLIT is approved by the FDA yet.

7. Future development and conclusions

There is a lack of suitable and safe formulations for pediatric populations. The difficulties in developing pediatric formulation are attributed to the diverse characteristics within this patient group with wide varying needs. Oral transmucosal delivery has several important advantages over the more conventional administration routes for children such as the oral and parenteral routes. Before a drug is investigated for the oral transmucosal formulation development, the physicochemical properties of the drug itself must fulfill a number of criteria, and there must also be a clear clinical benefit to make such an investigation worthwhile. The dosage forms must allow accurate dose measurement to children of widely varying age and weight. The ability of children to handle the dosage forms must be taken into consideration.

Although oral transmucosal route of administration has a great potential, there are knowledge gaps about this type of formulations for pediatric use, and further research in this area is absolutely necessary so that more patients could be benefited in the future. The three key areas for development include the dosage form acceptability, excipient safety and palatability. Special attention should be paid on the development of new solid dosage forms such as oral films and wafers which allow accurate dose measurement and easy administration. Safety is always a primary concern for all pediatric formulations including the use of excipient. Toxicity of commonly used pharmaceutical excipients may be attributed to the patients' insufficient metabolic capacity in their early years of life. This is an area that has been overlooked. Although the USA FDA has published a guidance for industry about the evaluation of pharmaceutical excipients, no safety levels of excipients for pediatric population have been defined. Taste masking technology for children is another area in need of investigation. The effect of palatability in pediatric formulation should not be underestimated, especially when the oral transmucosal formulations may require prolonged residence in the oral cavity. The European Paediatric Formulation Initiative (EuPFI) has formed working groups to address the safety use of pharmaceutical excipients and taste assessment methods for pediatric formulations. To achieve a rapid development of oral transmucosal delivery technology platform for pediatric formulations, collaboration between regulators, industry, practitioners and academia must be reinforced.

Declaration of interest

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