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Recent developments in buccal and sublingual delivery systems

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Introduction: There have been several advances in the delivery of drugs through the buccal mucosa over the last 5 years, which have resulted in a number of new buccal delivery products appearing on the market.

Areas covered: This review discusses the most recent developments in the area of buccal and sublingual drug delivery, with a focus on marketed drugs. Likely future directions are also considered and reported.

Expert opinion: The future potential of buccal and sublingual delivery systems looks favorable. It is envisaged that in the future, buccal and sublingual delivery technologies will provide a platform for the successful delivery of vaccines and antigens. It is also foreseen that physical means of enhancing drug uptake (e.g., sonophoresis, iontophoresis and electroporation) will be commercialized for buccal delivery, thereby expanding the current drug candidate list for this area. The formulation of delivery systems for photo-sensitizers in photodynamic therapy is a potential emerging area, while buccal and sublingual delivery, in general, is attractive for the development of intellectual property.

Keywords: allergen, buccal, buccal iontophoresis, orally dispersing tablets, oral films, sublingual, vaccine

1. Introduction

Since the publication of the last review article by the present authors [1], several important developments have occurred in the field of buccal delivery. These will be highlighted in this review as well as the developments on buccal and sublingual (s.l.) vaccine and allergen delivery. The reader is referred to the earlier review article for details of such items of basic science relevant to this topic as the structure of the mucosa, drug absorption pathways and reasons for utilizing the oral transmucosal route and so on. These will be mentioned only briefly in this article by way of introduction or if the description of a specific formulation or product requires it.

The previous review article ended on an optimistic note, predicting that more research and development of this route of drug delivery could be expected in future and some additional products that utilize the oral transmucosal route could be expected. There have been several new product introductions and several research publications describing the development of additional drug products to be administered by this route of administration. The reader may well ask: what major changes have occurred since the publication of the last review? These can be summarized as follows:

1) Many more orally disintegrating tablet formulations have appeared and a number of new supporting technologies have been developed to address the need for this type of product. The last few years have seen many excipient manufacturers offering 'directly compressible orally disintegrating matrix materials' for the pharmaceutical manufacturer to add to their drug and to

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Article highlights.

- Initial successes with buccal and sublingual delivery technologies with fentanyl products stimulated the development of additional products of this type, not only for pain treatment but also for the treatment of various disease conditions.
- Film strips and orally disintegrating tablets offer distinct advantages especially for geriatric or pediatric patients.
- Future opportunities exist to exploit the buccal and sublingual routes for the delivery of vaccines and antigens.
- The use of physical methods such as iontophoresis offers the opportunity to enhance drug transport through the buccal mucosa, which can appear on the market in the form of buccal drug delivery technologies.
- The formulation of systems for photosensitizers for photodynamic therapy is a potential emerging area for oral mucosal delivery.

This box summarizes key points contained in the article.

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aid tablet compression. With all these developments, orally disintegrating tablets have become much more commonplace.

2) Partly stemming from the above development, thin strips for buccal or s.l. delivery of drugs have come to the fore and are a growth area. So-called orally disintegrating tablets demonstrated that this type of dosage form is useful; then, due to the popularity, subsequently it became fairly commonplace, which stimulated researchers to find a follow-on technology.

3) The oral mucosal delivery of vaccines has become an area of great interest and research effort as well as the s.l. delivery of allergens.

4) Oral transmucosal formulations (initially Actiq and later Fentora) became therapeutic and financial successes, leading other companies to develop similar products.

This review will largely focus on these developments but will also mention some others that do not fall into these categories.

2. Orally disintegrating tablets

Orally disintegrating tablets (ODTs; which are also called orodispersible tablets, or orally dissolving tablets) dissolve or disperse within a few seconds after placement in the mouth without consumption of water. For the sake of the brevity, the ODTs will not be described in depth in this review. The reader is referred to the recent papers that extensively review the technologies [2,3]. The disintegrated material mixes with saliva and is easily swallowed in this form, thereby eliminating the difficulty in swallowing tablets or capsules experienced by some patients, children and seniors. For most drugs, absorption occurs subsequent to swallowing, in the post-esophageal section of the gastrointestinal tract. Since the drug is absorbed in this fashion, ODT cannot be considered buccal, or s.l.,

delivery systems. In these systems, the drug is released from a dosage form placed in the buccal cavity or under the tongue and the major portion of the drug is then absorbed by the buccal or s.l. mucosa. Since ODT are distinct from swallowed tablets, they are considered in this review to provide a complete discussion of dosage forms that are placed in the oral cavity and are not intended to be swallowed whole.

ODTs are considered a particularly useful dosage form for children and are likely to be the most suitable for developing countries. They are easy to administer, do not require additional water, and as the dispersion is fast, they cannot be spit out and can provide a range of dosages appropriate for use in young children [4,5]. A list of ODTs available in the US is given in **Table 1**, which is not intended to be comprehensive. In particular, generic ODTs were not included.

In addition to older technologies such as Orasolv, Durasolv (CIMA Labs) (formulated as compressed tablets), and Zydis (Cardinal Health) and Lyoc (CIMA Labs) (formulated as freeze dried wafers), WOWTAB (without water tablet) by Yamanouchi [6,7], several new technologies have appeared. Among them is the ADVATAB Technology by Aptalis [8], which uses a proprietary blend of ingredients formed into a soft granulation for rapid disintegration. In addition, these technologies offer taste masking through microencapsulation technologies. There is no magnesium stearate within the tablet to slow down disintegration and dissolution. Instead, lubrication is achieved by means of a modified tablet press, which sprays magnesium stearate onto the punches and dies immediately before the compression of each tablet. Hata and Fette are two companies offering equipment to manufacture tablets using external lubrication. The mechanism is part of the Hata press but Fette sells an add-on unit that can be fitted to almost any tablet press.

The principal challenge with ODTs is to develop formulations for standard direct compression processes that provide rapid disintegration, pleasant mouth feel and adequate tablet hardness to allow handling and transport. Superdisintegrants such as polyplasdone, croscarmellose sodium and sodium starch glycolate promote the rapid disintegration of the tablet and aid in the formulation of ODTs. In addition, proprietary blends of ingredients have now become available to facilitate compression of ODT. These blends contain all ingredients except the drug and lubricant and greatly ease the formulation of ODTs. Prosolv® ODT is an example of such an excipient [9]. It contains microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose and crospovidone. Another such excipient, Ludiflash® contains D-mannitol, crospovidone (Kollidon CL SF) and a polymer dispersion containing mainly polyvinyl acetate (Kollicoat SR 30 D) [10].

3. Oral film technology

The oral film technology or thin strip technology may be seen as an extension of ODT technology [11]. The latter development aims to expedite administration of drugs that

Table 1. Examples of orally disintegrating tablets available in the US.

Drug	Approval date	Product name	Manufacturer
Alprazolam	Jan 2005	Niravam	UCB, Inc.
Aripiprazole	June 2006	Abilify Discmelt	Otsuka America/Bristol-Myers Squibb
Carbidopa/Levodopa	Aug 2004	Parcopa	UCB, Inc
Clonazepam	Aug 2005	Klonopin Wafers	Roche Pharmaceuticals
Clozapine	Feb 2004	Fazaclo ODT	Azur Pharma International
Desloratadine	June 2002	Clarinex ODT	Schering
Donepezil hydrochloride	Oct 2004	Aricept ODT	Eisai, Inc
Lamotrigine	May 2009	Lamictal ODT	GlaxoSmithKline/Aptalis
Lansoprazole, Delayed Release	Aug 2002	Prevacid ODT	Takeda Pharma
Loratadine	Nov 2002	Claritin RediTabs	Schering Plough
Metoclopramide hydrochloride	Sept 2009	Metozolv ODT	Salix Pharmaceuticals
Mirtazapine	Jan 2001	Remeron SolTab	Organon USA, Inc./CIMA
Olanzapine	April 2000	Zyprexa Zydis	Lilly
Ondansetron hydrochloride	Jan 1999	Zofran ODT	GlaxoSmithKline
Phentermine hydrochloride	June 2011	Suprenza	Citius Pharmaceuticals, LLC
Prednisolone Sodium Phosphate	June 2006	Orapred ODT	Shionogi, Inc
Risperidone	April 2003	Risperdal ODT	Janssen Pharma
Rizatriptan Benzoate	June 1998	Maxalt-MLT	Merck & Co
Selegiline hydrochloride	June 2006	Zelapar	Valeant Pharmaceuticals International
Vardenafil hydrochloride	June 2010	Staxyn ODT	GlaxoSmithKline, Merck & Co, Bayer HealthCare
Zolmitriptan	Feb 2001	Zomig-ZMT	AstraZeneca/CIMA

were usually microencapsulated for taste masking in order to offer patients greater convenience. No water is needed for their administration. The oral thin strips could be seen as follow-on technology. Now, not only is the medication convenient to take, but also it does not become obvious, in a group setting that medication is being consumed. Originally used in the context of a breath freshener, drug manufacturers were quick to grasp the idea that it could be used usefully for medication. Chloraseptic relief strips, containing benzocaine for local effects, was launched by Zengen, Inc. in 2003. It was claimed, at that time, to be the first thin strip with a therapeutic agent [12]. In 2004, Novartis produced a series of thin strip dosage forms in its consumer division. The Triaminic and Theraflu thin strips series for the cough and cold market was claimed to be the first products of this type with a systemically absorbed drug. It is expected that the drug in these cases was largely absorbed through the gastrointestinal tract, and the administration of a thin film or strip was simply for the convenience of an easily administered dosage form. Thus, it can be seen that the thin strip may be used for local effects in the mouth and throat; or it may contain a drug that is released in the oral cavity, swallowed and then absorbed in the gastrointestinal tract; or it may be used as a delivery system for drug absorption in the oral cavity.

Monosol Rx has risen to become one of the leading US manufacturers of strip dosage forms with many of their Pharmfilm® product claiming to be absorbed via the buccal or s.l. mucosa, which will be described in the next section.

The thin strip has an area of usually no more than about 15 cm² (and often much less) and a thickness of 0.2 mm at

the maximum. Although larger films are possible, they will be less pleasant to use and the convenience of portability will be compromised. Hence, a disadvantage of thin strips is that it has the capacity to hold an even lower dose than ODTs. Indeed, one should not expect a drug loading of more than about 40 mg per strip at most, and usually a lot less. Novartis's Theraflu Nighttime Thin Strips contain 25 mg of diphenhydramine hydrochloride and 10 mg of phenylephrine hydrochloride, for a total drug loading of 35 mg [11,13]. In addition, extremely bitter drugs would be unpleasant by this route, taking into account, of course, the dose and the fact that flavors and sweeteners may be added. These disadvantages are balanced by the convenience and portability of the dosage form and its ease of administration.

There are two basic methods of making the strips: heat extrusion and film casting from a solution [11,13]. Generally, high-molecular-weight polymers create viscous gels from low concentrations of the polymer. When dried, the films are very thin. The high-molecular-weight polymers will result in tougher films but these may also be more brittle. The low-molecular-weight polymers, on the other hand, require more of the polymer to form a reasonably viscous gel and result in films that are thicker. They are also more flexible. Some formulations may require a combination of two viscosity grades of a polymer in order to create a film with the desired properties. Also several different polymers may be combined to create the ideal composition. For example, Listerine strips contain Pullulan, Carrageenan, Locust Bean Gum and Xanthan Gum (Consumer Information Database). Products based on thin strips that are currently available on the market are given in **Table 2**.

Table 2. Recently approved oral mucosal drug delivery systems.

Drug	Approval date	Mucosal site	Dosage form	Product name	Manufacturer
Fentanyl citrate	FDA Jan 2012	Sublingual	Spray	Subsys	INSYS Therapeutics
Fentanyl citrate	FDA Jan 2011	Sublingual	Tablet	Abstral	Orexo AB
	EMA Sep 2008				Prostrakan
Fentanyl citrate	FDA Sep 2006	Buccal	Tablet	Fentora	Cephalon
	EMA April 2008	Buccal	Tablet	Effentora	Cephalon
	Dec 2009	Sublingual			
Fentanyl citrate	FDA July 2009	Buccal	Film	Onsolis	Meda Pharmaceuticals, Inc
	EMA Oct 2010 (decentralized procedure)			Breakyl	
Zolpidem tartrate	FDA March 2009	Sublingual	Tablet	Edluar	Orexo AB
Zolpidem tartrate	FDA Nov 2011	Sublingual	Tablet	Intermezzo	Transcept Pharmaceuticals, Inc
Zolpidem tartrate	FDA Dec 2008	Oral	Spray	Zolpimist	ECR Pharmaceuticals Co., Inc
Buprenorphine and Naloxone	FDA Oct 2002	Sublingual	Tablet	Suboxone	Reckitt Benckiser
	EMA Sep 2006				
	FDA Aug 2010	Sublingual	Film		
Ondansetron	FDA July 2010	Oral	Film	Zuplenz	Strativa Pharmaceuticals
Asenapine	FDA Aug 2009	Sublingual	Tablet	Saphris	Schering-Plough Corp.*
	Sep 2010 (for new indication)				
	EMA Sep 2010	Sublingual	Tablet	Sycrest	H. Lundbeck A/S
Miconazole nitrate	FDA April 2010	Buccal	Mucoadhesive tablet	Oravig	BioAlliance Pharma
	UK and Denmark Jan 2008‡			Loramyc	
Midazolam	EMA Sep 2011	Buccal	Oromucosal solution	Buccolam	ViroPharma
Delta-9-tetrahydrocannabinol (THC) and Cannabidiol	Germany May 2011‡	Buccal, sublingual	Oromucosal solution	Sativex	Almirall, S.A. (ALM) and GW Pharmaceuticals

*Previously Merck & Co.
‡The first authorization granted date.
EMA: European medicines agency; FDA: Food and drug administration.

4. Buccal delivery systems

In recent years, a profound increase has been observed in studies on buccal delivery of drugs. Many different polymers are being investigated for this purpose besides the approved polymers such as carbomers and cellulose derivatives [14-17]. Among them are chitosan and its derivatives as well as the combinations of these polymers [18-20]. In this paper, we will focus only on the products available on the market for buccal delivery of drugs, which utilize different technologies. The list of the recently approved products is listed in **Table 2**.

The fentanyl Oralet™ was the first FDA-approved (1996) formulation developed to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children. The first product with a label claim for breakthrough cancer pain was fentanyl lollipop ('Actiq' by Anesta Corp., now Cephalon, Inc.), which received approval in 1998. The fentanyl effervescent buccal tablet, Fentora, was introduced by CIMA Labs/Cephalon in September, 2006, as the second fentanyl oral transmucosal dosage form [21,22] with an indication for breakthrough cancer pain. The fentanyl buccal tablet received approval from the European Commission in 2008 under the name of Effentora, a buccal tablet formulation of fentanyl. Effentora is indicated for the treatment of breakthrough cancer pain in adult patients who are already receiving maintenance opioid therapy for chronic pain. The approval allows Cephalon to market Effentora in the 27 member states of the European Union (EU), as well as Iceland and Norway. The proprietary OraVescent drug delivery technology was used to permit absorption of the opioid fentanyl across the buccal mucosa at a rate designed to match the onset of a breakthrough pain episode.

BioDelivery Sciences International, Inc. and Meda announced in 2010 approval of BEMA Fentanyl in Europe via the Decentralized Procedure, with Germany acting as Reference Member State. BEMA Fentanyl is indicated for the management of breakthrough pain in opioid tolerant, adult patients with cancer. BEMA Fentanyl, which is approved in the U.S. and Canada as Onsolis (fentanyl buccal soluble film), is marketed as Breakyl (fentanyl buccal film) in Europe. Breakyl is the first product to be approved in the EU using BEMA (Bio-Erodible MucoAdhesive) drug delivery technology, which consists of a small, bioerodible polymer film for application to the mucosal membranes (inner lining of cheek) [23]. BEMA films were designed to rapidly deliver a dose of drug across the mucous membranes for time-sensitive conditions or to facilitate administration of drugs with poor oral absorption. BioDelivery Sciences International, Inc. and Endo Pharmaceuticals recently announced (April 5, 2011) the completion of the BEMA Buprenorphine Phase III clinical trial, which assessed the efficacy and safety in the treatment of moderate-to-severe chronic pain [24]. These companies recently signed a worldwide license and development agreement for the exclusive rights to develop and commercialize BEMA Buprenorphine for the treatment of chronic pain.

Subsys is a sublingually administered single-dose spray formulation of fentanyl in a novel delivery device, which offers numerous benefits to patients who experience episodes of breakthrough cancer pain and very recently received approval by the FDA [25].

Abstral (Fentanyl) Sublingual Tablet (Orexo AB) is the first approved fast-acting and rapidly disintegrating formulation for breakthrough cancer pain in the US with the FDA mandated class Risk Evaluation and Mitigation Strategy (REMS) for transmucosal immediate-release fentanyl products. The product is now marketed by ProStrakan across the principal European markets [26].

Buccolam® (midazolam, oromucosal solution) (ViroPharma) was granted a Centralized Pediatric Use Marketing Authorization (PUMA) on September 2011, for treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents, from 3 months to less than 18 years of age. This action by the European Commission represents the first product approval through the centralized PUMA procedure since its inception. It is now approved throughout all the Member States of the European Union (EU) as well as in the European Economic Area (EEA), namely Norway, Iceland and Liechtenstein. Buccolam is oromucosal midazolam provided in a prefilled, age-specific dose formulation for convenient buccal (i.e., via the cavity between the cheek and gum) delivery.

Generex Oral-lyn™ is an investigational liquid formulation of regular recombinant human insulin that is delivered to the buccal mucosa using the RapidMist™ device. Insulin absorption is limited to the mouth with no entry into the lungs. This technology uses the formation of microfine, thin membrane, mixed micelles made from the combination of insulin and specific absorption enhancers that encapsulate and protect the insulin molecules.

Recently, Generex announced the results of their clinical studies on buccal delivery of insulin, which demonstrated that patients treated with the Generex Oral-lyn buccal insulin spray achieved a significant reduction of HbA1c compared with the control group, with no adverse events [27]. These preliminary results suggest that the addition of Generex Oral-lyn can be an effective treatment compared with diet and physical exercise alone in patients with impaired glucose tolerance in reducing HbA1c without adverse effects.

Sativex (Almirall, S.A. and GW Pharmaceuticals) is an oromucosal spray containing Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), medicine derived from cannabis, to be delivered to multiple sclerosis (MS) patients suffering from muscle spasticity [28]. The drug has recently been approved in Germany and Denmark for the relief of spasticity associated with MS. Sativex is also in Phase III clinical development in the US for the treatment of cancer pain, under its Investigational New Drug (IND) program.

A buccal dosage form of buprenorphine and naloxone was approved by the FDA as Suboxone buccal tablet, and recently its s.l. film form received approval, which is the second

FDA-approved drug based on MonoSol Rx's PharmFilm® Technology [29].

Intermezzo was approved in November 2011 for the new indication of middle-of-the-night insomnia [30]. Developed by Transcept Pharmaceuticals and to be marketed by Purdue Pharma, the s.l. tablet containing zolpidem tartrate is available in two strengths (3.5 and 1.75 mg) and may be taken when a middle of the night awakening results in difficulty in falling off to sleep again [31]. Due to the formulation that enhances s.l. permeation, the drug is rapidly absorbed through the s.l. mucosa, thus allowing the patient to fall off to sleep rapidly. Due to the low dose, the patient awakens after approximately 4 h, without undue daytime drowsiness. The product is also unique in that females are recommended a lower dose. In compliance with FDA requirements, the packaging is designed to emphasize that the drug should not be taken when there is less than 4 h bedtime remaining and to guard against the patient taking a second dose within a short time.

5. Buccal delivery by means of iontophoresis

Various chemical absorption enhancers and enzyme inhibitors have been used to make therapeutic drug delivery possible via the oral mucosal route and these enhancers have been extensively reviewed [32-35]. More recently, physical methods such as electric field and sonophoresis have also been used. The application of an electric field may provide an additional driving force on drug ions (iontophoresis), force water (or bodily fluids) to flow with the dissolved drug or metabolites or temporarily modify tissue structures to make them more permeable (electroporation) [36,37]. Such approaches may offer advantages by facilitating increased amounts of pharmacologically active compound to transport across the buccal mucosa; however, many technical issues need to be overcome, patient acceptance of the final dosage form needs to be evaluated and the potential improvement in patient compliance (especially of pediatric and geriatric populations) needs to be established before we witness widespread acceptance and use of this approach in the buccal drug delivery field.

The phenomenon of iontophoresis has been known for more than 100 years and has been widely applied in transdermal drug delivery. In recent years, it has also been investigated for enhancement of drug transfer across buccal mucosa [38-42]. The buccal mucosa provides an attractive area for electrical drug delivery. *In vitro* experiments have shown that buccal mucosa at pH 7.4 behaves as a cation exchange membrane and nonlinear resistor. It was reported to have a lower resistance and be more permeable to water than the skin. [36]. The anatomy of the buccal mucosa allows location of the electrodes set on the same surface. Another possibility is to place the donor electrode inside the cheek and the acceptor electrode on the external side of the cheek. This opposite location is suggested to increase the current efficiency of drug transfer [36]. The combination of drug delivery and metabolite

sampling in one device, and the use of the same driving force, is suggested to be very promising [37].

The enhancement effect of chemical enhancers and iontophoresis on the *in vitro* transdermal and transbuccal delivery of lidocaine hydrochloride, nicotine hydrogen tartrate and diltiazem hydrochloride was investigated using porcine skin and buccal tissues [43]. Dodecyl 2-(*N*,*N*-dimethylamino) propionate (DDAIP), dodecyl-2-(*N*,*N*-dimethylamino) propionate hydrochloride (DDAIP HCl), *N*-(4-bromobenzoyl)-*S*, *S*-dimethyliminosulfurane (Br-iminosulfurane) and azone (laurocapram) were used as chemical enhancers. It was shown that the application of iontophoresis at either 0.1 or 0.3 mA significantly enhanced delivery of the drugs with a more pronounced effect on transdermal delivery than on transbuccal delivery. In addition, DDAIP HCl was found to be the most effective enhancer for transbuccal delivery of lidocaine and nicotine. The combined treatment of iontophoresis and chemical enhancers was observed to provide limited synergistic effects on transdermal drug delivery and had no synergistic effect on transbuccal drug delivery [43].

A new class of delivery especially for chronic diseases, based on highly miniaturized computerized delivery systems integrated into a dental appliance, has been described in recent years [44,45]. An intraoral electronic device (IntelliDrug) for buccal delivery of naltrexone, which is an opioid antagonist widely used in the treatment of opiate addiction, alcoholism and smoking cessation, was developed [46]. It was shown to induce long-lasting, continuous and controlled levels of drugs in pigs, while avoiding the spikes observed typically in intravenous administration. For transbuccal delivery, galantamine, which is used for treating patients with mild-to-moderate Alzheimer's-type dementia, was loaded into the IntelliDrug device, and the permeation enhancement of the drug by iontophoresis was shown *in vivo* in pigs [47].

6. Sublingual vaccine delivery

The use of vaccines that induce protective mucosal immunity becomes very attractive when one considers that most infectious agents come into contact with the host at mucosal surfaces such as those of the respiratory, gastrointestinal and genital tracts [48]. Mucosal immunization, which is a noninvasive route, is an attractive alternative to parenteral immunization, and by using an appropriate delivery system, it is possible to stimulate both the mucosal and systemic immune responses [49,50]. Mucosal vaccination could be of tremendous advantage to less developed countries, which may not have cold storage facilities in place and also because of the far greater ease of administration, requiring less training of clinic staff. It lends itself to low-cost mass vaccinations. Of tremendous importance in areas with a high risk of infection is the fact that mucosal vaccines are needle-free and, therefore, the risk of needle reuse is eliminated.

However, poor immunogenicity and impaired antigen delivery with these systems still remain to be improved. Appropriate

vaccine formulations are needed to target mucosal inductive sites and also to prevent the antigen from physical elimination and enzymatic degradation. Adjuvants that are defined as molecules, compounds or macromolecular complexes that boost the potency and longevity of specific immune response to antigens [51] are commonly used in such formulations. The adjuvant may act as an immunostimulant or as a delivery system or it may combine both activities. The detailed description of these events is beyond the scope of this review; hence, the reader is referred to the recent papers that comprehensively review the vaccine adjuvants [49,52,51,53].

In recent years, there has been an increase in researches on the oral mucosa, specifically s.l. mucosa as a delivery route for vaccines [54]. Besides the noninvasive aspect of the delivery, the s.l. route provides advantage over other administration routes especially in infants and children in terms of simplicity, safety, volume required and consistency of outcome. It also avoids the hazards of digestion and concurrent diarrheal illness, which often reduces vaccine efficacy when delivered orally. The recent studies on s.l. vaccine delivery are summarized in **Table 3**.

Cuburu et al. [55] have shown that s.l. administration of ovalbumin (OVA), used as model antigen, together with the mucosal adjuvant cholera toxin (CT) induces both systemic and mucosal immune responses with cytotoxic T lymphocytes (CTL) and secretory antibodies in the genital tract, as efficiently as local intravaginal immunization. Afterward, it was reported that s.l. vaccination with inactivated influenza virus induces both systemic and mucosal immune responses and confers protection against a lethal intranasal (i.n.) challenge [56].

Current studies are focused on s.l. delivery of a vaccine against heterosexual transmission by human immunodeficiency virus (HIV) expecting to generate cytotoxic and antibody responses in the female genital tract and in extra-genital organs [57]. The findings of these studies emphasized the potential of the s.l. mucosa to serve as a potent route of vaccine delivery for inducing protective genital antibody and cellular immune responses, which would limit the genital transmission of HIV-1. Cuburu et al. [58] have sublingually immunized the mice with human papillomavirus (HPV)-like particles using cholera toxin as the adjuvant and showed a protection against a genital challenge with HPV pseudovirions.

In another study, s.l. immunization with HIV-1 gp41 and a reverse transcriptase polypeptide coupled to the cholera toxin B subunit (CTB) was shown to induce gp41-specific IgA antibodies and antibody-secreting cells, as well as reverse transcriptase-specific CD8 T cells in the genital mucosa, contrary to intradermal immunization [57].

The s.l. administration of a vaccine containing the recombinant major outer membrane protein from *Chlamydia trachomatis* mouse pneumonitis (CT-MoPn) against *C. trachomatis*, which causes respiratory and sexually transmitted infections [59]. Different administration routes (intramuscular (i.m.), subcutaneous (s.c.), s.l. and colonic (c.l.))

were used for comparison. The adjuvants CpG and Montanide were used for systemic routes, i.m. and s.c., and cholera toxin for mucosal routes, s.l. and c.l. Mucosal immunizations were performed either alone or in combination with systemic routes. Following the i.n. challenge, the best protection was obtained with the s.l. + i.m. + s.c. showing that a combined systemic/mucosal vaccination would provide better protection against a respiratory challenge with *C. trachomatis* than either systemic or mucosal immunizations alone.

Effects of vaccine administration route, mucosal and systemic immune responses against human papillomavirus 16 L1(HPV16L1) protein were studied using i.n., intravaginal, transdermal, s.l. and i.m. routes. The s.l. route was reported to provide the most effective mucosal secretory IgA and serum IgG responses. To enhance the immunogenicity of s.l. vaccines, the adjuvanticity of nine molecules three toll-like receptor agonists, three nucleotide-binding oligomerization-domain agonists, vitamin D3, poly-γ-glutamic acid and cholera toxin subunit B (CTB) was also investigated. Among the molecules tested, the most enhanced mucosal sIgA and systemic IgG induction was obtained with CTB [60].

The 40-kDa outer membrane protein of *Porphyromonas gingivalis* (40k-OMP) sublingually administered with a cDNA vector plasmid encoding Flt3 ligand (pFL) was shown to elicit a protective immune response with significantly induced serum IgG and IgA, as well as salivary IgA, antibody titers. It was concluded that s.l. administration of 40k-OMP with pFL acts as an effective and safe mucosal vaccine against oral *P. gingivalis* infection and may be a useful tool in the prevention of chronic periodontitis [61].

The efficacy of s.l. immunization with *Bacillus subtilis* engineered to express tetanus toxin fragment C (TTFC) was studied by Amuguni et al. [62] in comparison with i.n. immunization. A nontoxic mutant of *Escherichia coli* heat-labile enterotoxin (mLT) was included as adjuvant. Protective IgG antibodies against tetanus toxin challenge were obtained with s.l. administration as well as high IgA levels in saliva, vaginal wash and feces. It was reported that, at least in the case of tetanus, for both s.l. and i.n. immunizations, the inclusion of the adjuvant mLT was detrimental. This was attributed to antigenic competition or conflicting adjuvant activities of *B. subtilis* and mLT. Adjuvant activity was found to be evident when TTFC expressed in *B. Subtilis* [62].

A new nutritive immune-enhancing delivery system (NIDS) composed of vitamin A, a polyphenol-flavonoid, catechin hydrate and mustard oil was tested for its adjuvant effect in immune responses against the gp120 protein of HIV-1$_{CN54}$. Following a combination of mucosal (i.n./s.l.) and systemic (i.m) vaccinations of mice, a significant enhancement in both local and systemic antibodies as well as cytokine responses was obtained [63].

The effectiveness of s.l. delivery of two different viral vectors: a recombinant adenovirus (rAd5), and a Herpes Simplex Virus Type-1 amplicon vector (HSV-1) was studied in

Table 3. Studies on sublingual vaccine delivery.

Antigen	Adjuvant/delivery system	*In vivo* studies	Response	Ref.
Ovalbumin	Cholera toxin	Female BALB/c, C57BL/6 mice, DO11.10 BALB/c mice	Induced vigorous systemic and mucosal antibody responses	[55]
Formalin-inactivated Influenza A/PR/8 virus (H1N1)	mCTA-LTB	Female BALB/c mice, Polymeric Ig receptor knockout (pIgR−/−) mice, MyD88−/− mice	Induced both systemic and mucosal antibody responses and conferred protection against a lethal intranasal (i.n.) challenge with influenza virus	[56]
			Heterosubtypic protection against respiratory challenge with H3N2 virus	
Live influenza A/PR/8 virus (H1N1)	mCTA-LTB		Induced systemic expansion of IFN-α-secreting T cells and virus-specific cytotoxic T lymphocyte responses	
Porphyromonas gingivalis (40k-OMP)	DNA plasmid encoding FL (pFL)	Female BALB/c mice	Induced immune responses to prevent oral infection by *P. gingivalis*	[61]
Ovalbumin	Cholera toxin	Female BALB/c C57BL/6 mice	Induced antigen-specific IgG and IgA in blood and in cervicovaginal secretions	[58]
HIV-1 gp41	Cholera toxin B subunit	Female BALB/c mice	Induced B- and T-cell immune responses comprising secretory antibodies and cytotoxic CD8 T cells in the mouse genital tract	[57]
Reverse transcriptase polypeptide coupled to the cholera toxin B subunit (CTB)			Conjugation of the reverse transcriptase peptide to CTB favored cross-presentation by human dendritic cells to a T cell line from an HIV+ patient	
Tetanus toxoid	*E. coli* Heat-Labile enterotoxin (LT)	Female BALB/c mice	Induced mucosal and systemic immune responses	[86]
	Mutant of LT lacking ADP ribosyltransferase activity (LTK63)		LT-treated mice showed significantly higher responses compared with LTK63 immunized mice	

40k-OMP: 40-kDa outer membrane protein of *Porphyromonas gingivalis*; mCTA/LTB: Subunit of mutant cholera toxin E112K combined with the pentameric B subunit of heat-labile enterotoxin from enterotoxigenic *Escherichia coli*.

Table 3. Studies on sublingual vaccine delivery (continued).

Antigen	Adjuvant/delivery system	In vivo studies	Response	Ref.
Human papillomavirus 16 L1 (HPV16L1) protein	Toll-like receptor (TLR) agonists: poly(I:C), imiquimod monophosphoryl lipid A (MPL); Nucleotide-binding oligomerization-domain (NOD) agonists: murabutide peptidoglycans (PGN) muramyl dipeptide with a C18 fatty acid chain (L18-MDP); γ-polyglutamic acid; Vitamin D$_3$; Cholera toxin B subunit	Female BALB/c mice	Sublingual route provided the most effective mucosal secretory IgA (sIgA) and serum IgG responses	[60]
Chlamydia trachomatis mouse pneumonitis (CT-MoPn)	Cholera toxin	Female BALB/c mice	Combination of the sublingual and intramuscular + subcutaneous routes for immunization resulted in more robust protection than vaccinating only by the intramuscular + subcutaneous routes	[59]
Bacillus subtilis cells expressing tetanus toxin C fragment	mLT (mutant heat labile toxin from enterotoxigenic *E. coli*)	Mice	Induced protective systemic immune response, boosted mucosal secretory IgA and IgG antibody levels and balanced Th1/Th2 response	[62]
gp120 protein of HIV-1$_{CN54}$	Nutritive immune-enhancing delivery system (NIDS) composed of vitamin A, a polyphenol-flavonoid, catechin hydrate and mustard oil	Female BALB/c mice	Enhanced serum and vaginal antibody responses	[63]
Adenovirus serotype 5-based HIV-Gag (Ad5-HIV-Gag)	–	Male C57BL/6 mice	Induced antigen-specific cytotoxic T-lymphocyte responses in both the systemic and the mucosal compartments	[65]
Adenovirus serotype 5 vector expressing HIV-1 envelope glycoprotein (HIV-1$_{MN}$ gp120)	–	Female BALB/c mice	Elevated levels of HIV-1 envelope glycoprotein-specific serum IgA, and vaginal IgA and IgG	[64]
Herpes Simplex Virus Type-1 amplicon vector (HSV-1) expressing HIV-1 envelope glycoprotein (HIV-1$_{MN}$ gp120)			Robust antigen-specific antibody responses in plasma and in vaginal washes with adenovirus serotype 5 encoding HIV-1 envelope glycoprotein (Env) but no specific antibodies with HSV-1 amplicon vector encoding HIV-1 Env	

40k-OMP: 40-kDa outer membrane protein of *Porphyromonas gingivalis*; mCTA/LTB: Subunit of mutant cholera toxin E112K combined with the pentameric B subunit of heat-labile enterotoxin from enterotoxigenic *Escherichia coli*.

mice [64]. The s.l. delivery of an rAd5 encoding HIV-1 envelope glycoprotein (Env) was found to show robust antigen-specific antibody responses in plasma and in vaginal washes, whereas s.l. delivery of an HSV-1 amplicon vector encoding HIV-1 Env was not able to elicit Env-specific antibodies. It was demonstrated that s.l. delivery of an Env-encoding rAd5 vector could elicit a potent antigen-specific mucosal antibody response without the presence of an adjuvant. The ability of an rAd5 vector to efficiently penetrate the s.l. epithelium and to elicit an immune response against an encoded transgene is consistent with work recently reported by Appledorn *et al.* [65], who showed for the first time that a recombinant [E1-]Ad5-based HIV vaccine vector expressing HIV-Gag can induce antigen-specific CTL responses in both the systemic and the mucosal compartment following s.l. vaccination.

The findings of the studies performed on animal models suggest that the s.l. delivery route is effective and safe. It allows protective immune responses by non-replicating antigens or inactivated and live virus and enhances systemic IgG and mucosal IgA antibodies and CTL responses. Yet there are still hurdles to overcome in regard to s.l. administration, including the development of mucosal adjuvants and improved formulations that would enable enhanced efficacy and lowered dose. Formulations with enhanced mucoadhesion and permeation are required for higher efficacy of s.l. vaccines in humans. These properties will help to maintain an intimate and prolonged contact of the formulation with the s.l. mucosa and facilitate the uptake of the vaccine antigens.

A randomized double-blind placebo-controlled study was conducted to determine the effect of s.l. administration of interferon-α (IFN-α) on the immune response to influenza vaccination in elderly institutionalized individuals. Sublingual administration of 10 million IU of IFN-α immediately prior to vaccination was shown to reduce the geometric mean hemagglutination inhibitory (HAI) and IgG2 circulating antibody titers, and the secretory IgA (sIgA) response in saliva, to the New York strain of influenza A virus, 21 days post-vaccination, without detectable drug-related local or systemic toxicity. At the dose tested, s.l. administration of IFN-α reduced the immune response to influenza vaccination in elderly institutionalized individuals [66].

The s.l. route has been widely used for immunotherapeutic treatments of allergy. Sublingual immunotherapy (SLIT) is a form of immunotherapy that involves administering the allergen extracts either in liquid or tablet form under the tongue, which is an alternative treatment to allergy shots [67,68]. This form of immunotherapy has been used for years in Europe and recently has had increased interest in the US. However, it is currently not approved by the FDA. Multiple studies are currently being conducted for the purpose of trying to get SLIT approved in the US [69,70]. SLIT has been endorsed by The World Health Organization (WHO) as an alternative to injection therapy [71]. SLIT is considered safe and effective [72] and is more convenient than allergy shots.

Furthermore, SLIT is an ideal means of treating the pediatric population because of its safety, tolerable adverse effects and good compliance [73,74].

Grazax 75000 SQ-T oral lyophilisate (ALK-Abello A/S, Denmark) is an s.l. preparation, which contains an allergen extract of grass pollen to treat rhinitis and conjunctivitis caused by grass pollen in adults and children (5 years or older) [75]. Grazax is commercially available in various countries within Europe.

Oralair 100 IR and 300 IR s.l. tablets (Stallergenes) received European approval through a mutual recognition procedure, for the treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titer of the specific IgE to the grass pollen. Germany, the first country where Oralair has been marketed, was the Reference Member State.

The value of mucoadhesive formulations to enhance SLIT efficacy has been shown in a therapeutic murine model [76]. Recently, a European project (FP-7-SME) [77] was granted to develop a new innovative mucoadhesive chitosan-based adjuvant, Viscogel, and to show its safety and efficacy in prophylactic and therapeutic vaccination. Preclinical proof-of-concept for Viscogel-Bet v 1 formulations for s.l. allergy therapy will be investigated.

7. Buccal mucosa and photodynamic therapy

In the last part of this review, another method to utilize the oral mucosa for drug delivery will be briefly mentioned. This approach, photodynamic therapy (PDT) and photodynamic antimicrobial chemotherapy (PACT), which involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen to kill target cells [78,79]. PDT, which is accepted to be minimally invasive and minimally toxic, is used clinically to treat a wide range of medical conditions of oral mucosa including neoplastic and non-neoplastic conditions. PACT has been shown to eradicate a wide variety of pathogens of the oral cavity, thus this treatment is considered as an alternative for the management of infections that respond poorly to conventional antibiotics and antifungal therapy. In the future, this approach may play an important role in persistent infections [80-83].

For the delivery of the photosensitizer in the oral cavity, the right formulation has an important influence on the outcome of the therapy. The size of the photosensitizer molecule, its pH and lipophilicity affect its transport to the site of action. The solubility and diffusivity of the molecule, and its chemical stability, are also important factors for efficient delivery. Furthermore, the rate of drug release as well as the contact time of the delivery system on the mucosa will influence the availability of the drug. An optimized system should provide ease of application and be acceptable by the patient. On the

other hand, the photosensitizers used can be highly colored, which would result in staining of teeth, lips and buccal mucosa. Suitable formulations that provide targeted delivery of the photosensitizer to the site of infection are required [84]. A wide range of organisms from the Gram-positive *Staphylococcus aureus* to the Gram-negative *Pseudomonas aeruginosa* have been shown to be susceptible to PACT with a number of different photosensitizers *in vitro* [85]. However, no clinical treatments based on PACT are currently licensed.

8. Conclusion

There have been several recent advances in recent years in the area of buccal and s.l. drug delivery that have led to the commercialization of products and their appearance on the market. Many have exploited the fact that a delivery system administered to, and located on, buccal or s.l. mucosa can release its drug into the oral cavity and then be swallowed for subsequent absorption along the gastrointestinal tract. Recently, there have been several successful commercializations of technologies that utilize this approach and that offer advantages to the consumer in terms of convenience and ease of use. Since the oral cavity offers the advantage of easy access to apply the delivery system to the young, we have witnessed buccal or s.l. products appearing on the market aimed at facilitating drug administration and delivery to pediatric patients. On the down side, technologies developed and commercialized for use in the oral cavity are still limited by low bioavailability and small drug loadings. These limitations restrict the list of drug candidates that can be incorporated into buccal and s.l. drug delivery technologies.

Reports in the literature suggest that future opportunities exist to exploit the buccal and s.l. routes for the delivery of vaccines and antigens. Similarly, the use of physical methods to drive drugs through the buccal mucosa (e.g., sonophoresis, iontophoresis and electroporation) offers the opportunity to enhance drug transport through the buccal mucosa. This could lead to such technologies appearing on the market in

the form of buccal drug delivery technologies. Finally, this review has highlighted that PDT appears to offer future potential for this route of drug delivery.

9. Expert opinion

The oral cavity remains an attractive site for drug delivery. Recent advances in technology development have become evident. Film strips and ODT offer distinct patient advantages that have resulted in their popularity. Such advantages include ease of transport and storage; the need for very little water to dissolve the tablets or films; and ease of use in a patient range that encompasses geriatric or pediatric patients. While initial successes with buccal fentanyl products stimulated the development of additional products of this type, the future may see other drugs delivered through the oral mucosa for breakthrough cancer pain and, possibly, for other forms of pain as well as for other disease conditions. The future potential of buccal and s.l. delivery systems looks favorable. It is envisaged that in the future, buccal and s.l. delivery technologies will provide the platform for the successful delivery of vaccines and antigens. It is also foreseen that physical means of enhancing drug uptake (e.g., sonophoresis, iontophoresis and electroporation) will be commercialized for buccal delivery thereby expanding the current drug candidate list for this area. The authors also believe that the formulation of delivery systems for photosensitizers in PDT is a potential emerging area, while buccal and s.l. delivery, in general, is attractive for the development of intellectual property.

Declaration of interest

I Pather was previously employed by the following companies, and has been involved in developing the following products: Fentora (Cima Labs), Intermezzo (Transcept Pharmaceuticals, Inc.), orally disintegrating tablets (Cima Labs and Aptalis). All other authors declare no conflict of interest.

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