Expert Opinion

Current status and the future of buccal drug delivery systems

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Background: The delivery of drugs through the buccal mucosa has received a great deal of attention over the last two decades, and yet there are not many buccal delivery products available on the market. *Objective*: This review outlines the advantages and disadvantages of buccal drug delivery, provides a historical perspective and discusses representative developmental and marketed drugs. *Methods*: The structure of the oral mucosa is briefly described to preface a description of the pathways for drug absorption and a critical discussion of permeation experiments. A brief historical perspective followed by a description of some of the currently marketed products provides a picture of where we are today. An indication is given of likely progress in this area and of the attributes of a successful business entity of the future. *Conclusion*: The authors provide an assessment of the future potential of buccal and sublingual drugs.

Keywords: bioavailability enhancement, buccal delivery, mucoadhesion, mucosa, peptides, permeability, transmucosal

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1. Introduction

The delivery of drugs through the oral mucosa, especially the buccal and sublingual mucosa, has received a great deal of attention for several years. This interest has stimulated many academics to perform basic research dealing with drug permeation through the oral mucosa. The mechanistic approach of these researchers led to the study of permeation enhancers and mucoadhesion. In addition, several pharmaceutical companies are actively involved with the development of oral transmucosal drugs, either as a sole delivery mechanism or as one of many routes that are exploited. This article explores the reasons for developing such dosage forms, their advantages and disadvantages. It also reviews the pertinent research and development issues, some recent successes and drugs in development.

2. Advantages and disadvantages

There are many reasons why the buccal mucosa might be an attractive site for the delivery of therapeutic agents into the systemic circulation. The accessibility of the oral cavity makes application of drugs easy and acceptable to the patient, that is the dosage form can be attached without any pain and discomfort, while permitting easy removal in the event of adverse reactions. It is a well vascularized tissue and the blood vessels drain directly into the jugular vein [1]. Therefore, drugs penetrating the epithelium are delivered directly into the systemic circulation, thus avoiding the hepatic first pass effect and hydrolysis in the gastrointestinal tract. The buccal mucosa provides an environment almost free from the acidity and protease activity encountered elsewhere in the gastrointestinal tract. The cellular turnover time in the buccal region of the oral cavity is estimated to be 4 – 14 days [2], which is intermediate between the slow turnover rate of

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the skin and the fast gastrointestinal rate. In view of this, a mucoadhesive device may be worn for many hours or even days without disturbing its adhesion due to rapid cell division. In addition, fairly rapid recovery is possible if slight tissue damage occurs due to wearing a dosage form. An often overlooked advantage is that the microenvironment of a dosage form placed in the oral cavity can directly and easily be modified. Thus, the physicochemical conditions in a small volume of biological fluid can be changed with minimal side effects, in contrast to altering the conditions in a large fluid compartment.

However, there are also disadvantages associated with this route of drug delivery, mainly the low permeability and a smaller absorptive surface area in comparison to the absorptive surface area of the small intestines [3]. Additionally, the continuous secretion of saliva (0.5 – 2 L/day) leads to subsequent dilution of the drug. Salivation and resulting swallowing effectively remove the drug from the preferred absorptive region. Conversely, for patients secreting too little saliva ('dry mouth syndrome'), there may be insufficient saliva for dissolution to occur at the desired rate. The taste of the drug may also present difficulties to patients and decrease compliance with the dosing regimen. This problem may be greater with certain patient populations such as the young, the elderly and patients experiencing nausea either due to their illness or as a consequence of concomitant medications. If the buccal delivery system is mucoadhesive, movements of the mouth or tongue may displace or otherwise affect the dosage form adversely. Moreover, the hazard of choking by involuntarily swallowing the delivery system is a concern, in addition to the inconvenience of such a dosage form when the patient is eating or drinking. Where a dosage form is to be held for any length of time in the oral cavity, with the instruction to avoid swallowing, the dosing instructions may not be accurately followed by some patient populations, for example the young, the elderly and some physically or mentally impaired patients. If food or liquid consumption occurs post-application of mucoadhesive dosage forms, the temperature and pH of the consumed material may affect drug release. For some drugs, mucositis may be a contraindication to the use of oral transmucosal dosage forms due to potentially faster absorption and pain at the site of application. These are some of the problems that are associated with buccal drug delivery and they should be carefully weighed against the advantages when a decision has to be made concerning the route of delivery for a new product.

3. Mucoadhesives and penetration enhancers

The ability to maintain the delivery system at a particular location for an extended period of time has great appeal for both local disease treatment as well as systemic drug bioavailability. Utilization of mucoadhesive polymers is essential to maintain an intimate and prolonged contact of the formulation with the oral mucosa. The long contact time allows a longer duration for absorption. Some adhesive systems deliver the drug towards the mucosa only with an impermeable product surface exposed to the oral cavity [4]. Another approach to assure therapeutic levels of a drug via the buccal route is to incorporate a penetration enhancer into the formulation.

A drug may be placed in a sustained release (SR) matrix because it is only slowly absorbed through the oral mucosa. Ideally, the release rate from the matrix should be less than, or equal to, the absorption rate of the drug through the mucosa. If this is not the case, the excess drug (the amount of drug released in unit time that is greater than that absorbed through the oral mucosa) would be lost to swallowing. Furthermore, in order to provide an incremental improvement in the absorption rate of a drug that is inherently slowly absorbed, a penetration enhancer may be added to an SR matrix.

The SR matrix is usually used in conjunction with a mucoadhesive so that the dosage form is held in one location while it slowly releases its drug content. The SR matrix material may simultaneously provide mucoadhesion and, thus, only one additive is necessary. Alur *et al.* used the polysaccharide exudate from the plant Hakea gibossa as both the SR matrix material and mucoadhesive [4].

Mucoadhesive polymers as well as penetration enhancers used for buccal delivery have been extensively reviewed by several authors in recent years [5,6]. The brevity of the current article precludes their description here, but readers are referred to these reviews for information.

4. Structure of the oral mucosa and routes of absorption

A familiarity with the structure of the oral mucosa is required to understand how drugs, after being released from pharmaceutical products placed in the oral cavity, cross the mucosa for penetration into blood capillaries. Since this topic has been extensively described by several authors, only pertinent information to facilitate the discussion will be mentioned here. The reader is referred to these documents for a more detailed account [1,7,8].

The oral mucosa, in regions of the mouth subject to the mechanical forces associated with mastication, is covered by a keratinizing epithelium resembling that of the epidermis of the skin. The mucosa in such regions, for example the gingiva (gums) and hard palate, is known as masticatory mucosa. The mucosal lining of the floor of the mouth and buccal regions, which must be flexible so as to accommodate chewing or speech, is termed a lining mucosa and is covered with a non-keratinizing epithelium closely resembling the epithelium covering the esophagus or uterine cervix [9].

The epithelium arises from a basal layer of cuboidal cells. From this actively dividing layer, cells are pushed upwards to the surface and become more flattened as they reach the

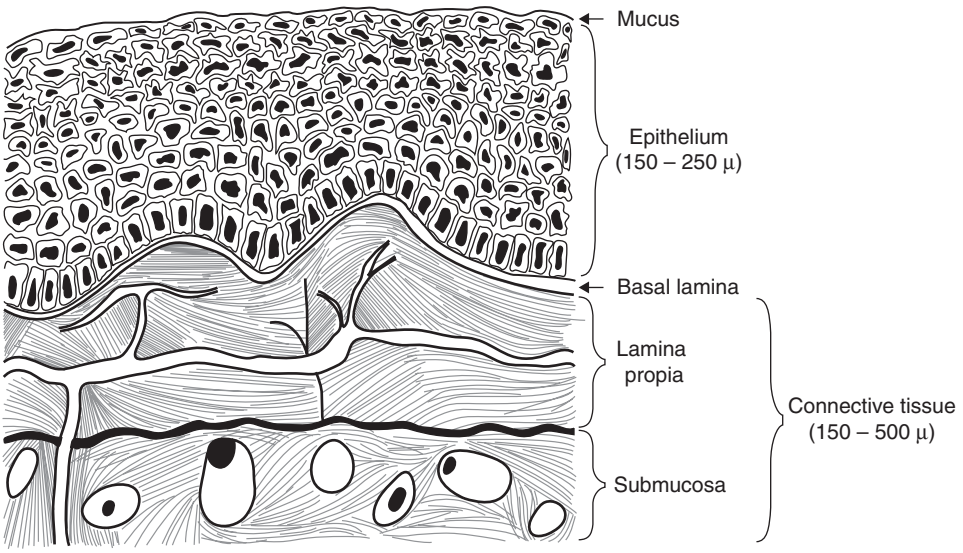

Figure 1. Structure of the buccal mucosa.
Artwork: Jayd Pather.

uppermost layers, which are described as squamous, stratified cells. The epithelium consists of 40 – 50 layers, only a few of which are shown in the diagrammatic representation depicted in **Figure 1**. The epithelium protects the underlying tissue from mechanical and chemical injury. The mechanical barrier enables us to chew on rough food while the chemical barrier prevents noxious chemicals from directly entering the systemic circulation (as previously mentioned, blood flowing from the oral cavity bypasses the liver). The efficiency of this chemical barrier is one of the major obstacles to the development of oral transmucosal delivery systems: the function of the epithelium is to keep out foreign chemicals, whereas the aim of transmucosal delivery is to enable selected foreign chemicals (known as drugs) to permeate this tissue and reach the bloodstream.

The connective tissue supports the epithelium and consists of a lamina propria and submucosa, as shown in **Figure 1**. The lamina propria contains a network of capillaries. It is difficult for drugs to permeate the tightly bound cell layers, especially the outermost layers, of the epithelium. However, once a drug has permeated through the layers of cells constituting the epithelium and the basement membrane, it can easily penetrate the capillaries and enter the general blood circulation. Hence the epithelium is the barrier to drug permeation. In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue must be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. Developers of a buccal drug delivery system containing penetration enhancers should address the biological issues including permeability, enzymatic degradation and compatibility [10].

The constancy of the oral environment is ensured to a large extent by the continual secretion of saliva into the oral cavity from the three major salivary glands and numerous minor salivary glands located in, or beneath, the mucosa. Saliva, by continually bathing the surface of the oral mucosa, maintains a moist atmosphere and a stable but slightly acidic pH. Compared to the secretions of the gastrointestinal tract, saliva is a relatively mobile fluid with less mucin, limited enzymatic activity and virtually no proteases.

The basic drug transport mechanism for the oral epithelium is the same as for other epithelia in the body. There are two major routes involved: the transcellular route (directly through the cells, or intracellularly) and the paracellular route (through the spaces between the cells, or intercellularly) [11]. These routes are illustrated in **Figure 2**. In general, for many drugs, permeation across the buccal epithelium is thought to be through the paracellular route by passive diffusion. This pathway is favored especially by hydrophilic drugs such as peptides/proteins which dissolve more readily in the aqueous fluids filling the intercellular spaces. The transcellular pathway, in contrast, involves drugs permeating the cell membrane and going through the cell to then penetrate the opposite cell membrane and into the next cell, and so on, as shown in **Figure 2**. An example of a drug known to penetrate via the transcellular pathway is fentanyl [12]. It is feasible that some drugs may penetrate via both pathways and this may occur with drugs that have approximately balanced hydrophobic and hydrophilic properties, with a slight predominance of hydrophobicity. Such drugs will usually penetrate the fastest. Most often, however, one pathway predominates. In addition to these major pathways, other transport mechanisms (e.g., carrier-mediated transport)

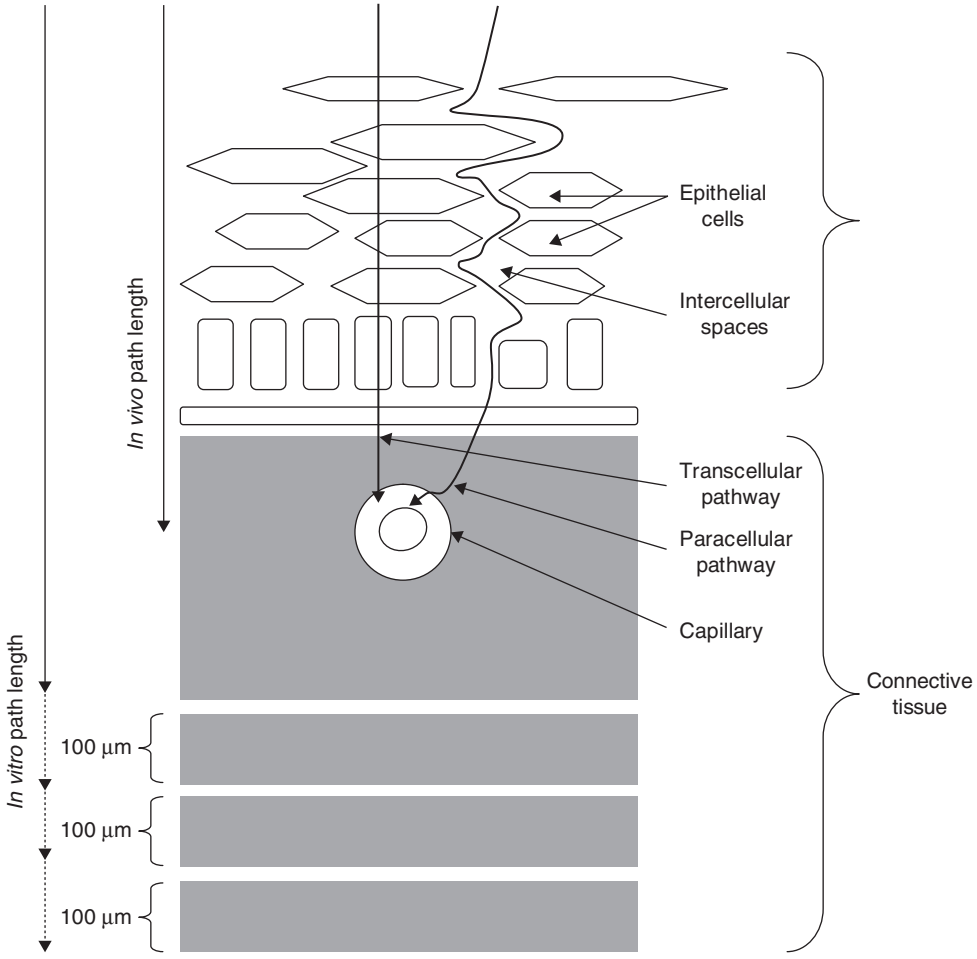

Figure 2. Diagrammatic representation of pathways for drug delivery through the oral cavity mucosa showing the direct transcellular and tortuous paracellular pathways; and the *in vivo*, and longer *in vitro*, path lengths.

play a role in the transport of some drugs across the oral mucosa [13].

It can readily be seen that the transcellular pathway is a more direct pathway, with drugs tending to move directly across the cell layers with little lateral diffusion. For the paracellular pathway, the drug moves in a tortuous fashion around the cells, thus this is a longer pathway. It is important to make the following distinction: while the shortest pathway that the drug may take around the cells is longer than the transcellular pathway, there is also a greater tendency, in paracellular permeation, for the drug to diffuse laterally over a wider area of the mucosa. This may help to explain the longer lead time (the time until steady-state absorption occurs) often observed with drugs that are known to be absorbed by the paracellular pathway. Caffeine is an example of a drug absorbed via the paracellular route and it is used as a marker of paracellular absorption [14].

While the transcellular route is more direct, the drug has to traverse the lipophilic cell membrane, then the hydrophilic interior of the cell before passing through two cell membranes to reach the cytoplasm of the next cell. Therefore, the predominantly hydrophobic drug should have some hydrophilicity if absorption into the systemic circulation is required. If the drug is extremely hydrophobic, there would be a tendency for it to be retained in the more hydrophobic components of the mucosal tissue, such as the cell membranes of the superficial epithelial layers, and not reach the blood circulation in significant amounts. This, of course, would be a desirable feature for a topical effect (e.g., anti-inflammatory action) but not if a systemic effect is desired.

5. Progress in buccal delivery systems

A recently published book [15] lists 93 companies involved with drugs delivered to the oral cavity, with many companies developing multiple drugs. This list includes companies developing orally disintegrating tablets (ODT). Even if one were to exclude (for the reasons stated below) those companies involved solely with ODT, there would remain

many companies intensely researching oral transmucosal drug delivery. Furthermore, the search term 'buccal delivery' at the United States Patent and Trademark Office website [16] reveals 126 patents that were issued between 1976 and July 2007. A search at the esp@cnet database [17] revealed seven patents in Europe and 127 worldwide. While some of these patents make only an oblique reference to buccal delivery, many of the inventions are primarily related to this route of administration, indicating that novel buccal formulations are being actively conceptualized and invented. The combination of academic and industrial research represents a significant investment of time and resources in this route of drug delivery.

In contrast to the fairly extensive research outlined above, a computer database search indicates that there are less than 50 registered products available for buccal/sublingual delivery in the US at the time of writing [18]. Many of these are multiple presentations of the same drug, such as different flavors and strengths of nicotine chewing gum. Thus, not many active pharmaceutical ingredients (APIs) have successfully reached the marketplace as drugs for oral transmucosal delivery. Some of these, such as nicotine and nitroglycerine, have been used in buccal/sublingual delivery dosage forms for many years. There is, thus, a disparity between the intense research activity over the last two decades and the drugs for oral transmucosal delivery actually reaching the market. This disparity will be addressed later.

It is important to distinguish orally disintegrating tablets (ODT) from transmucosal dosage forms. The latter release the drug for absorption through the oral mucosa. An absorption enhancer can be incorporated to aid drug absorption. ODT, on the other hand, are generally not intended for oral mucosal absorption. Instead, the drug-containing coated microcapsules (or other units) are released from the dosage form into the oral cavity, usually after rapid disintegration of the tablet. The microcapsules are then swallowed and the major portion of the drug is released distal to the oral cavity when the coating dissolves. The purpose of the coating is to prevent the patient experiencing the bad taste of the drug, since the barrier coating retards the drug's dissolution. Since the major portion of the drug is not absorbed through the oral mucosa, ODT should not be considered buccal or sublingual delivery systems.

For rapid oral transmucosal delivery, the drug may be presented as lozenges, patches, sprays, or compressed tablets having a fairly rapid in-mouth disintegration time (15 min or less). Where prolonged action is required, the dosage form is usually mucoadhesive (patch or mucoadhesive tablet) and the drug is released slowly for slow absorption through the oral mucosa. Nagai [19] was among the first to pioneer the bioadhesive drug delivery system in the early 1980s. The first product developed by him contains a steroidal anti-inflammatory, triamcinolone acetonide, and is still on the market for the treatment of aphthous stomatitis (AFTACH; Teijin Pharma, Japan) [20].

There is no evidence that the thin films currently marketed (mostly for OTC products) deliver the drug through the oral mucosa, but research is ongoing for such an application [21,22]. While bite capsules that release a drug solution have been described in the patent literature [23-25], the authors are not aware of a commercial product using this dosage form. In contrast to what is commonly believed by the lay population, there is also no evidence that homeopathic products placed in the oral cavity deliver the active ingredient through the oral mucosa.

The first recorded use of oral transmucosal delivery (sublingual) appears to be an 1879 paper [26] describing the use of glyceryl trinitrate for the treatment of angina. This drug penetrates the mucosa easily and does not require any enhancement. In spite of this early success, not much further development of the sublingual and buccal routes occurred during the next 70 – 80 years.

The fentanyl Oralet™ is 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. Some have argued that opioids administered to children should have a disagreeable taste, precluding the use of this oral transmucosal drug delivery system [27]. On the other hand, taste remains one of the major determinants of mucosal contact time and is of particular importance for products especially designed for children. Fundamental limitations associated with this mode of administration are the lack of cooperation of children, their difficulties in coordination, and the risk of choking and aspiration. The accuracy of dosing is also a key problem, since oral mucosal dosage forms may be swallowed or spat out prior to sufficient absorption taking place. The applicability of these dosage forms in the treatment of paediatric patients generally depends on the age of the child.

In 1998, the fentanyl transmucosal lozenge ('Actiq' by Anesta Corporation, now Cephalon) was introduced to the market. This was the first product labeled for breakthrough cancer pain, although other products had previously been used off label for this purpose. The fentanyl effervescent buccal tablet, Fentora, was introduced by CIMA LABS/ Cephalon in September 2006 as the second fentanyl oral transmucosal dosage form [28,29] with an indication for breakthrough cancer pain. The product is suitable for this purpose since significant blood levels are attained within 15 min [28]. It should be remembered that fentanyl is not well absorbed through the gastrointestinal tract. Reference [28] provides a description of the *in situ* conversion of fentanyl citrate to fentanyl free base, which is the more lipid-soluble form of the drug. The latter permeates the lipid cell membrane easily, leading to rapid drug absorption. For this reason the effervescent dosage form has a much higher bioavailability than the same dose of Actiq, a point which prescribers and pharmacists should be aware of in view of the serious side effects of fentanyl, the most noteworthy being respiratory depression.

Cephalon announced that the company has filed a marketing application with the European Agency for the Evaluation of Medicinal Products (EMEA) for this product in Europe. If approved, the centralized filing of this application would allow Cephalon Europe to market this product in 29 European countries. The tablet is placed in the buccal cavity (above a premolar, between the gum and the cheek) where it disintegrates over approximately 10 min, releasing the drug. Cephalon is currently researching the use of this product for other pain indications such as breakthrough neuropathic pain [30]. Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, this product is contraindicated in the management of acute or postoperative pain. Since the amount of fentanyl contained in these preparations can be fatal to children, great care should be taken to restrict the access of these medications to children.

In 2002, the FDA approved Subutex (buprenorphine) for initiating treatment of opioid dependence (addiction to opioid drugs, including heroin and opioid analgesics) and Suboxone (buprenorphine and naloxone) for continuing treatment of addicts. The naloxone is intended to be a safeguard against the intravenous injection, by drug abusers, of the active ingredient in this transmucosal dosage form. Suboxone is the only centrally acting product approved for the treatment of opioid dependence in the European Union (EU). These drugs were introduced by Reckitt and Colman in an attempt to address the wave of opioid abuse sweeping Europe and America.

Reckitt and Colman also introduced prochlorperazine buccal tablet (Buccastem) in Europe and in certain other countries such as Japan for the treatment of nausea and vomiting. The tablet is placed in the buccal area where it releases the drug over a few hours. BioDelivery Sciences International (BDSI) acquired the rights to develop prochlorperazine buccal tablets (Emezine) in the US from Reckitt Benckiser (previously Reckitt and Colman). However, BDSI received a non-approvable letter from the FDA in March 2006 for the company's new drug application for Emezine [31]. The slower absorption in the first 1 – 2 h (compared to the oral swallowed tablet) observed in the pharmacokinetic studies submitted with the new drug application (NDA) caused the FDA to be concerned about onset of action. The higher C_{max} values seen in these studies led the FDA to question the drug's impact on older patients and, therefore, the FDA has requested a study in this population group. The company reported that it was in the process of developing the pharmacokinetic protocols that will be presented to the FDA under a special protocol assessment [32].

Oral mucosal testosterone has been shown to be useful to elevate male hormone levels, avoiding the degradation that occurs in the gastrointestinal tract and due to the first pass effect through the liver. Striant (Columbia Pharmaceuticals) is a buccal system approved by the FDA in 2003. It offers a novel treatment option for the 4 – 5 million men who require testosterone replacement therapy for a deficiency or absence of endogenous testosterone associated with hypogonadism.

Miconazole Lauriad 50 mg bioadhesive buccal tablets (Loramyc, BioAlliance Pharma SA) were approved in October 2006 by France's regulatory body, AFSSAPS, for the local treatment of oropharyngeal candidiasis in immunodepressed patients, particularly those with head and neck cancers who have undergone radiotherapy and those infected with HIV. Loramyc (miconazole) is formulated using the company's patented Lauriad drug delivery technology which permits the tablet to adhere to the mucosal membrane, and thus allows delivery through early and extended release of the therapeutic agent onto the site of the disease. Miconazole Lauriad is currently being evaluated in pivotal Phase III clinical trials in the USA, Canada and South Africa. The company reported that the same technology is being used to develop a second product (acyclovir Lauriad) for the treatment of oral herpes.

In August 2007, Health Canada approved a new indication for a cannabis-derived pharmaceutical buccal spray, Sativex (GW Pharmaceuticals; marketed by Bayer, a subsidiary of Bayer AG). The new indication is the adjunctive analgesic treatment of moderate-to-severe pain in adult advanced cancer patients already being treated for persistent background pain with the highest tolerated dose of a potent opioid. This product was previously approved by Health Canada (in 2005) as adjunctive treatment for the symptomatic relief of neuropathic pain in adults with multiple sclerosis. Sativex is currently undergoing late stage clinical development in Europe and the US. Once approved in the UK, Bayer will also market Sativex in that country. Upon approval in Europe, Sativex will be marketed by Almirall, whereas in the US it will be marketed by Otsuka.

Buccal–midazolam (Epistatus) (currently unlicensed) is becoming an accepted option for the treatment of status epilepticus and serious tonic–clonic seizures in community settings in the UK [33]. This treatment option is advocated by the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN). It is more convenient to use, and less embarrassing for the child, than rectal diazepam, the previous treatment of choice. However, the introduction of this liquid buccal formulation a few years ago has raised the possibility of dose confusion, as it is twice the strength of the injection that was initially used for this purpose.

The products described above are summarized in **Table 1**. Let us now turn our attention to how drugs, after being released from pharmaceutical products placed in the oral cavity, cross the mucosa for penetration into blood capillaries.

6. Permeation studies

The permeability of buccal epithelium and the efficacy of penetration enhancers have been investigated in numerous *in vivo* and *in vitro* models. Since such studies may be a key

Table 1. Commercially available oral mucosal drug delivery systems.

Drug	Mucosal site	Dosage form	Product name	Manufacturer
Fentanyl citrate	Buccal	Lozenge	Actiq	Cephalon
	Buccal	Tablet	Fentora	Cephalon
Buprenorphine hydrochloride	Buccal	Tablet	Subutex	Reckitt Benckiser
Buprenorphine hydrochloride-naloxone HCl	Buccal	Tablet	Suboxane	Reckitt Benckiser
Proclorperazine	Buccal	Tablet	Buccastem	Reckitt Benckiser
Triamcinalone	Buccal	Tablet	Aphtac	Teijin Ltd
Testosterone buccal	Buccal	Tablet	Striant SR	Columbia Pharmaceuticals
Nitroglycerine	Sublingual/ Buccal	Tablet, Spray	Nitrostat	W Lambert-P Davis-Pfizer Pharmaceuticals
Glyceryl trinitrate	Buccal	Spray	Nitromist	NovaDel
	Buccal	Tablet	Suscard	Forest Laboratories
Nicotine	Buccal	Chewing gum	Nicorette	GSK Consumer Health
	Buccal	Lozenge	Nicotinelle	Novartis Consumer Health
Miconazole	Buccal	Tablet	Loramyc	BioAlliance Pharma SA
Cannabis-derived	Buccal	Spray	Sativex	GW Pharmaceuticals, PLC

component of the overall development of buccal products, an overview of this work is presented.

Beckett and co-workers demonstrated in humans that the loss of drug from a solution held in the mouth can be attributed to oral mucosal absorption [34,35]. Swallowing and salivation can be accounted for by the changes in volume and concentration of a red dye in the original, and the expelled, solutions. A series of papers from Beckett's laboratory in the 1960s and 1970s demonstrated the buccal absorption of different drugs and the fact that the pH of the solution influences the absorption of many drugs. In later research, specially designed cells containing drug solutions which were affixed to the oral mucosa of a variety of test animals were used [36]. In some instances, perfusion cells were used in human volunteers. These models have been comprehensively reviewed by Rathbone *et al.* [37].

This type of experiment has largely been supplanted by the *in vitro* model in which a drug is allowed to pass from a donor cell through a piece of excised mucosa to the receiver cell. The concentration of the drug in the receiver cell is measured at fixed time intervals to determine the time course of permeation. It is usual to use a surrogate for human oral mucosal tissue, such as porcine buccal tissue, in such experiments. In countries where the use of pigs is not culturally acceptable, bovine buccal tissue with a non-keratinized epithelium has been used for permeability studies [38,39].

The tissue may be excised from sacrificed animals or the local abattoir may provide a ready supply. Such experiments are commonly performed in the course of developing oral transmucosal dosage forms. However, the results of such experiments do not always lend themselves to unambiguous interpretation. Therefore, it may be useful to review the basic technique and some of the issues and common misconceptions.

For perfusion studies, buccal mucosa has been mounted on various kinds of diffusion cells, including continuous flow perfusion chambers, side-by-side chambers (Ussing chambers and Grass-Sweetana cells) and vertical diffusion cells (Franz cells). A drug solution of known concentration is transferred to the donor cell and a physiologically compatible solution is added to the receiver cell. The receiver chamber is sampled at fixed intervals and assayed for the drug that has been transferred through the membrane up to that point.

The apparent permeability coefficient is determined from the slope of the linear portion of the permeation versus time plot, using Equation 1.

$$P_{app} = (dC_r / dt) \times V_r / (A \times C_0) \quad (1)$$

where,

P_{app} is the apparent permeability coefficient,

dC_r/dt is the slope of the cumulative concentration in the receiver compartment versus time plot,

V_r is the volume of the receiver compartment,

A is the surface area of buccal epithelium available for permeation, and

C_0 is the initial concentration of the compound on the donor side.

Variations in the tissue preparation method can lead to differences in the observed permeation rate. Each laboratory should, therefore, standardize its method of tissue excision and preparation. Differences in preparative methods should also be taken into account when comparing results from different laboratories. It is best to use fresh membranes whenever possible, as the method of storage of the membrane can also lead to observed differences in the permeation rates. In a comparative study of tissue storage methods, antipyrine and caffeine permeability values were used [40]. A storage method was deemed acceptable if similar permeability values were seen for the stored membrane and for the freshly excised tissues. The damage to the membranes due to freezing is worth noting, as many authors have previously used frozen membranes for permeation studies [41,42].

The use of integrity markers and positive controls in the experiment is vital. Transepithelial electrical resistance (TEER) is a method of assessing the integrity of the membrane. If there are minute tears in the membrane, the electrical resistance between the donor and receiver cells is altered. This test should be conducted before and after the permeation experiment. The first test confirms that no damage to the membrane occurred during tissue preparation and experimental set up, while the latter test confirms that the drug treatments did not compromise the integrity of a membrane that was acceptable to start with. It is good practice to include in the donor cells, together with the drug of interest, a compound known to have low permeability (such as Lucifer yellow) and a high permeability compound (such as caffeine) as markers of the level of membrane permeability. Caffeine is known to be rapidly, and completely, permeable through oral mucosa *in vivo* [14].

Replicated experiments of the identical set up (same drug, concentration, enhancer and experimental conditions) may show variability as high as 20 – 50%. With two sets of data, each with this extent of variability, it is often difficult to make a meaningful comparison where there is only a moderate difference in permeability. The sources of this variability are many and include, first, the animals themselves, which are subject to normal biological variation (a few experiments/replicates may be done with tissues from the same animal), their age and condition being important. Then there are the differences in the method of tissue excision and preparation, and method of storage, if the tissue is not used immediately. Therefore, when conducting these experiments, observe all the precautions mentioned.

Scientists new to the technique may be surprised that it takes longer for the drug to permeate the isolated tissue than it does *in vivo*. Thus, significant blood levels may be observed much faster than the *in vitro* experiment would indicate. This difference will be observed even when the absorption mechanism is known to be passive diffusion. The *in vitro* experiment merely provides the rank order of permeation rates of a series of compounds or the rank order of the efficacy of a series of enhancers, not an indication of the absolute permeation rates *in vivo*. In view of this, dose ranging studies would still have to be done during clinical development of the product. Part of the explanation for this phenomenon is the fact that in a live animal, the blood flow through the capillaries, found in the connective tissue just below the basement membrane, provides perfect sink conditions. The absence of blood flow may make a significant difference to the rate of drug permeation through the excised mucosa. Related to this is the fact that in a live animal the drug must penetrate only as far as the capillaries for absorption to occur, whereas in an isolated tissue experiment the drug must further traverse the connective tissue to reach the receiver cell. This longer pathway is depicted diagrammatically in **Figure 2**. The thickness of the connective tissue may vary between experiments, thus adding a variable additional path length for diffusion. This may have an impact on the results, as explained below.

While the epithelium has been correctly stated to be the major impediment to drug diffusion, the role of the connective tissue in excised membranes may have been under-rated, since no specific mention is made of controlling its thickness in several publications, examples of which are references [43,44]. In a recent study, the permeability of antipyrine and caffeine were shown to be inversely proportional to tissue thickness [45]. An increase of about 100 µm significantly decreased the permeability of these compounds ($p < 0.05$). It is evident that differences in tissue thickness are the result of variations in the thickness of the connective tissue attached to the epithelium, since the latter is consistent between samples. It is imperative that each laboratory validate their tissue excision, preparation and handling methods in order to achieve the most consistent and reliable results.

The temperature at which the experiment is conducted and the analytical methods used are the additional sources of error. The permeability of model compounds through excised porcine buccal mucosa was found to increase exponentially with temperature [46]. Sensitive analytical methods are required, considering the small volumes of the receiver compartment and the analytical sample.

Recently, cultured epithelial cell lines have been developed as an *in vitro* model for studying drug transport and metabolism and barrier properties, as well as to elucidate the possible mechanisms of action of penetration enhancers. Non-keratized buccal cells (EpiOral™) plated in 6-well plates may be obtained from MatTek Corporation [47]. The use of these tissue plates involves a cost greater than that associated with obtaining excised buccal tissue from the local abattoir.

As an alternate model, human vaginal tissue has been used in permeation experiments as a surrogate for buccal tissue with apparent success [48]. Human vaginal tissue is more easily available than human buccal tissue as some vaginal tissue may be excised during hysterectomies. Vaginal and buccal tissues share some structural similarities, making this a viable alternative tissue [49]. Of course, legal and

Table 2. Some oral transmucosal products in development in the US.

Company	Products	Dosage form
Generex	Insulin, 'Ora-lyn'	Oral spray (RapidMist) technology
	Low MW Heparin	
	Fentanyl	
	Morphine	
NovaDel	Sumatriptan	Lingual spray technology
	Zolpidem	
	Ondansetron	
Biodelivery Sciences International (BDSI)	BEMA Fentanyl	Mucoadhesive disc
	BEMA LA (long-acting analgesics)	
	BEMA Zolpidem	
	Prochlorperazine	
Transcept Pharmaceuticals	Zolpidem	Sublingual lozenge (Bimucoral technology)

ethical considerations must be paramount in the decision to use human tissues for any experiment.

Some of the drugs currently in development will now be briefly discussed, mentioning some of the difficulties encountered. An overview of such issues (where the information is in the public domain) provides a better understanding of the complexities of the development process.

7. Buccal delivery systems in development

Research and invention has been fairly active in this area, especially during the last decade. Some of the products known to be in development are shown in **Table 2**. The ongoing research and development is expected to yield at least a few successes in the form of products approved for marketing.

Two studies comparing the effects of zolpidem oral transmucosal spray and Ambien tablets (healthy volunteers and elderly healthy volunteers) were completed by NovaDel in 2007 [50]. On 23 January 2008, the company announced that the FDA has accepted, for filing, its NDA for ZolpiMist™ (zolpidem tartrate) Oral Spray for the short-term treatment of insomnia. NovaDel's nitroglycerine lingual spray (Nitromist™) for the treatment of angina was approved by the FDA in November 2006 [51]. NovaDel's licensee for the Ondansetron buccal spray, Hana Biosciences, announced in February 2007 that there were issues with precipitation from the solution during stability studies of scaled-up batches [52]. NovaDel stated that this obliged a change in formulation and/or scale-up, and that this issue would set the Ondansetron program back to some extent [53]. In August 2007, NovaDel announced a sublicense agreement with Par Pharmaceutical [54] in terms of which NovaDel and Par would collaborate on the reformulation of the ondansetron spray, while Par was responsible for updates to the NDA and commercialization activities in North America. Par and Hana Biosciences entered into a separate licensing agreement.

Transoral Pharmaceuticals (now known as Transcept Pharmaceuticals) successfully completed a low dose zolpidem Phase III sleep laboratory study of a sublingual lozenge [55]. The study showed that the product was effective at approximately one-third the standard dose in treating middle-of-the-night (MOTN) awakening, a poorly managed sleep problem. There were also no residual side effects. It is suggested that it may provide physicians a useful patient-controlled low dose treatment for middle-of-the-night insomnia. Since it is low dose (3.5 mg) and is only taken on the nights that it is required, it offers the potential to reduce unnecessary medication. Patients who suffer primarily from awakenings in the middle of the night must, at the present time, take medication at bedtime and may be medicating themselves more often than required. The company is completing a second Phase III study in out-patients and expects to submit an NDA in 2008 (55).

Generex has done extensive work on oral mucosal delivery of insulin and their product is marketed in South America [56]. The registration in 2005 in Ecuador is believed to be the first marketing approval in the world of a non-injectable insulin. It was approved for the treatment of type 1 and type 2 diabetes. The company's RapidMist device is used to supply a fine mist to the mouth. 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. It is claimed that the absorption is limited to the mouth with no entry into the lungs. A once-a-day long-acting injection is still needed, but the multiple injections associated with meals are avoided [57]. A Phase III study is expected to be started by the end of 2007 with patient enrollment in the US, Europe and Canada, and US marketing approval is anticipated by 2009 [58].

Recently, Fertin Pharma A/S and Generex Biotechnology Corporation established a collaboration for the development of a metformin medicinal chewing gum for the treatment of type 2 diabetes mellitus and obesity [59]. The smaller dose of buccally administered drug is expected to reduce the gastrointestinal irritation and bloating caused by metformin.

8. Why is the development and approval of these dosage forms so slow?

There may be several reasons which, when taken together, represent a fairly large challenge.

1. Often, these are low dose drugs with special characteristics which may present formulation difficulties

such as content uniformity issues, difficulty in attaining very fast dissolution or, conversely, attaining steady, sustained release over a predetermined time. The achievement of the optimal formulation may be difficult for the drug in question (the dosage form is often either very rapidly releasing, or it may have a combination of sustained release and mucoadhesive properties).
2. There needs to be a good understanding of the underlying biology and permeability issues and the complexity of these questions may be underestimated.
3. There is often a need to have a special mechanism to enhance the absorption of the drug without causing undue side effects.
4. The taste of the drug and patient acceptability may be a problem.
5. While an increase in the absorption rate and an enhancement of bioavailability are both desirable attributes, the extent of improvement may have been underestimated during early development. Dose titration for *in vivo* studies may prove to be difficult.
6. With a novel route of administration, it may be more difficult convincing regulatory agencies of the acceptability of a new product. The agency may display greater circumspection, in keeping with their aim of protecting the public.
7. Oral transmucosal delivery research and dosage form development are often undertaken by smaller companies who do not have the resources of the larger pharmaceutical companies. This may become a significant issue, noting the other difficulties mentioned in this section.

These difficulties may help to explain the difference between the extent of research activity and the number of buccal drugs actually reaching the marketplace.

9. Conclusion

This article describes the development of buccal delivery dosage forms, the background to such development and some of the issues and problems. Representative successes have been mentioned, in addition to describing some of the drugs currently in development. Many of these are expected to be successfully developed and to receive marketing approval. It must be borne in mind that careful selection of drugs is required for successful transmucosal delivery. In the first place, buccal/sublingual delivery must offer a definite therapeutic advantage for it to be useful. Examples of a therapeutic advantage are: reducing the first pass effect, or the faster attainment of clinically relevant blood levels. Where buccal delivery allows the avoidance of more intrusive delivery mechanisms, such as injections, it would also be useful. It is ideal for drugs that are not absorbed in the GIT or those that are largely destroyed in the GIT. The delivery of peptides by this route would be a major advantage since it avoids injections. Developing robust, scalable products that meet these criteria is not straightforward. However, research and development with this objective is being actively pursued. While there are challenges to be faced, several new buccal delivery products are expected to be available for clinical use in the near future.

10. Expert opinion

Initial development successes by established companies, sometimes with the collaboration of universities, may encourage research by new entrants into the field and stimulate more vigorous development by existing players. Further successes are likely to lead to some opportunistic entrants into this field.

There may also be some consolidation, mergers, or acquisitions by the companies involved. This has already happened to some extent. For example, Cephalon acquired both Anesta Corporation and CIMA LABS. Each company had developed its own fentanyl oral transmucosal technology. The acquisition by Biodelivery Sciences International (BDSI) of Arius Pharmaceuticals in 2004 [60] is another example.

Apart from acquisitions, other forms of cooperative agreements between the small companies engaged in this field may occur in order to leverage the strengths of each other. For example, Arius acquired an exclusive worldwide license to the BEMA technology of Atrix Laboratories in 2004 [61]. This license probably made Arius a better acquisition target for BDSI. In the terms of the agreement, Atrix retained the right to co-promote BEMA fentanyl. NovaDel entered into development agreements with both Hana Biosciences and Par Pharmaceutical for the co-development of Ondansetron buccal spray. Cooperative agreements are likely to increase both in number and in scope in the future. Areas that are ripe for cooperation include formulation development, scale-up, packaging development (novel, robust, patient-friendly packaging is often needed to maintain the innovative dosage forms in a stable manner), regulatory submissions, clinical development and marketing.

An open-minded approach is required by the companies or consortiums that are likely to succeed. Companies with an innovative attitude or who foster innovative thinking amongst their scientists and give them the freedom to explore novel ideas will eventually be the commercially successful ones in this area. Alongside the company approach, good patent counsel and a willingness to devote resources to patent understanding would enhance the uptake of commercialized products. Additionally, a company in this area would benefit from a proactive Regulatory Affairs Department that not only complies with regulations but can also champion a case-by-case approach to develop and defend a strong regulatory argument for options chosen by the company in regulatory gray zones.

It is significantly easier and cheaper to modify the route of administration and/or the indication of an existing drug,

whose biological characteristics are well understood, than it is to develop a new chemical entity (NCE). This is partly due to the reduced need to study the toxicology and side effects of a well-known drug in a new formulation. In view of this, greater reliance should be placed on improving the delivery of currently marketed drugs in the future. Such enhanced, innovative, non-painful and non-threatening delivery systems must offer a definite therapeutic improvement. With such an approach, the twin objectives of enhanced therapy and improving the bottom line of companies may be achieved. In this light, oral transmucosal delivery may be one of the delivery mechanisms that become important in the future. Exciting challenges remain and their resolution will provide stable, patient-friendly dosage forms that allow the manipulation of the bioavailability of drugs across the oral mucosa.

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