

Chapter 2

Overview of Oral Mucosal Delivery

Michael John Rathbone, Indiran Pather and Sevda Şenel

2.1 Introduction

The oral cavity is an attractive site for the delivery of drugs either locally or directly into the systemic circulation. Its attractiveness resides in the fact that the mucosal membranes, upon which drug delivery systems are located, are readily accessible to patients or their carers. This means that the delivery technology can be precisely placed on the specific oral cavity membrane that is chosen as the site of absorption. It also means that the delivery system can be removed in order to terminate delivery if signs of adverse reactions are observed during treatment. The oral cavity represents a challenging area to develop an effective drug delivery technology. This arises due to the various inherent functions of the oral cavity (eating, swallowing, speaking, chewing), as well as the presence of the fluid that is involved in all these activities, saliva. This fluid is continually secreted into, and then removed from, the mouth. There are many advantages and disadvantages associated with the oral cavity as a site for drug delivery. Overall, however, it remains a viable option as a route for drug administration and has been extensively studied for that purpose [1–7].

In this chapter, the rationale behind companies pursuing the goal of developing oral mucosal drug delivery systems as well as the key considerations in the design and development of a drug delivery system intended for use in the oral cavity will be discussed. Finally, this chapter will briefly describe some of the formulation aspects of delivery systems that have been successfully developed to deliver drugs via this route.

M. J. Rathbone (✉)
ULTI Pharmaceuticals Ltd., Hamilton, New Zealand
e-mail: michael.john.rathbone@gmail.com

I. Pather
College of Pharmacy, California Northstate University, 9700 West Taron Drive,
Elk Grove, CA 95757, USA
e-mail: i.pather@yahoo.com

S. Şenel
Faculty of Pharmacy, Hacettepe University, Ankara, Turkey
e-mail: ssenel@hacettepe.edu.tr

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2.2 Reasons for Developing Oral Mucosal Drug Delivery Systems

Table 2.1 lists the advantages, while Table 2.2 lists the disadvantages of the oral cavity as a site for drug delivery. These tables have been constructed from information adapted from published reviews written by the present authors [1–7]. A perusal of these tables suggests that there are as many disadvantages as there are advantages for using the oral cavity as a site for drug delivery. Table 2.1 shows that the oral cavity is an attractive site for the delivery of drugs either locally or directly into the systemic circulation. Ultimately, the decision to utilize the oral cavity as a site for drug delivery should be based on a comparison to other sites of delivery with regard to the following parameters: the clinical objectives of the treatment, the inherent physicochemical properties of the drug, the relative advantages of the route, product differentiation opportunities, the patient population, the cost of production and R&D time.

2.3 Key Considerations in the Design and Development of Oral Mucosal Drug Delivery Systems

2.3.1 Influence of Oral Cavity Anatomy and Physiology on Drug Delivery

The anatomy and physiology of the oral cavity have a direct influence on the design of oral mucosal drug delivery systems. The anatomy and physiology have been comprehensively dealt with in a separate chapter of this book. This section provides a summary of the positive and negative influences of the various physiological and anatomical features of the oral cavity that may influence oral mucosal drug delivery system design and evaluation. These are compiled in Table 2.3.

2.3.2 Drug Absorption Across the Oral Mucosa

Two major routes of absorption are involved in oral mucosal drug permeation: the transcellular or intracellular route (where drugs permeate directly through the cells) and the paracellular or intercellular route (where drugs permeate by passive diffusion through the spaces between the cells) [11]. The paracellular route is favoured especially by hydrophilic drugs such as peptides/proteins which dissolve more readily in the aqueous fluids filling the intercellular spaces.

An example of a drug known to penetrate via the transcellular pathway is fentanyl [12], which is a highly lipophilic drug, whereas an example of a drug absorbed via the paracellular route is caffeine [13], which is a water-soluble drug.

Table 2.1 Advantages of the oral cavity as a site for drug delivery

Aspect	Advantage	Comment
Accessibility	The different sites in the oral cavity are easily accessible	This property increases patient convenience. Furthermore, the precise placement of the delivery system at any site in the oral cavity allows the targeting of a specific membrane, thus differentiating the different oral cavity routes
Administration	The ease of accessibility referred to above means oral mucosal drug delivery systems are easy to administer	This property increases patient acceptability for oral mucosal drug delivery systems
Removal	The ease of administration is matched by the ease of removal	Useful property in the event of adverse reactions. Delivery can be easily terminated if side effects from the drug are observed
Patient acceptability	Highly acceptable site for drug delivery by the patient	This site for drug delivery is well accepted by the patient, increasing patient compliance
First-pass effect	The oral mucosa is a well vascularized tissue and the blood vessels drain directly into the jugular vein [8]	Drugs penetrating the epithelium are delivered directly into the systemic circulation, thus avoiding the hepatic first-pass effect
Avoidance of gastrointestinal tract environment	Drugs absorbed across oral mucosa directly into the systemic circulation	Direct absorption of drugs into the systemic circulation avoids hydrolysis in the gastrointestinal tract. Swallowing of dissolved drug should be avoided
Enzymatic barriers	The buccal mucosa provides an environment with reduced peptidase and protease activity	Significantly less drug metabolism is seen in the oral cavity
Cellular turnover time	The cellular turnover time of the oral mucosa is estimated to be 4–14 days [9]. This is intermediate between the slow turnover rate of the skin and the fast gastrointestinal rate	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 [7]
Microenvironment	The microenvironment of a dosage form placed in the oral cavity can directly and easily be modified	The physicochemical conditions in a small volume of saliva that bathes the oral mucosa at the site of administration can be changed with minimal adverse effects

Table 2.2 Disadvantages of the oral cavity as a site for drug delivery

Aspect	Disadvantage	Comment
Membrane permeability	In general, oral cavity mucosa shows low permeability to drugs	Membrane thickness varies from a few hundred micrometres for the sublingual region to 500 μm for the buccal mucosa
Surface area	The surface area of the oral cavity is small; it is approximately 214 cm^2 [10]	The oral cavity has a smaller absorptive surface area compared to the small intestines
Saliva	Saliva is continually secreted into the oral cavity from major and minor salivary glands	The continuous secretion of saliva (0.5–2 L/day) can lead to dilution of the drug or excessively fast erosion of a dosage form. For patients secreting too little saliva (dry mouth syndrome), there may be insufficient saliva to allow dissolution of the drug
Swallowing	Salivation leads to swallowing which effectively removes drug from the target site of absorption	Efficacy of the drug would change and side effects would increase
Taste receptors	The tongue contains taste receptors that may present difficulties to patients and decrease compliance with drugs that are bitter	This problem may be greater with certain patient populations such as the young and the elderly
Membrane flexibility	Some of the oral mucosa (e.g. sublingual and buccal mucosa) is flexible and flexes as a consequence of normal functions of the mouth (e.g. speaking, chewing or swallowing). This may adversely affect the dosage form	If the oral mucosal drug delivery system contains a mucoadhesive, movements of the mouth or tongue may dislodge the dosage form from the site of administration
Choking hazard	Involuntarily swallowing of the delivery system could lead to choking	This potential hazard should be considered during the design of the delivery system and evaluated during the research or development phase
Inconvenience	A buccal delivery system may cause inconvenience to the patient when they are eating or drinking	If food or liquid consumption occurs post application of, say, a mucoadhesive dosage form, the temperature and pH of the consumed material may affect drug release
Tissue irritation	For some drugs, tissue irritation may arise following the use of an oral mucosal drug delivery system	Irritation may lead to faster absorption and/or pain at the site of application
Drug candidates	Drug candidate list is small	The list of drugs that can be incorporated into oral mucosal drug delivery systems is limited due to low permeability of the mucosa which results in low bioavailability, and the small drug loading capacity of the delivery systems. Also, salivation and swallowing remove drug from the absorption site

Table 2.3 The influence of physiological and anatomical features of the oral cavity on drug delivery system design and evaluation [1–7]

Aspect	Advantage	Disadvantage
Saliva	Promotes dissolution of drug	Constant secretion and removal by swallowing can cause drug and delivery system to be removed from the intended site of absorption
	Wets dosage forms containing mucoadhesives, thereby promoting adhesion to the oral mucosa	
	Saliva continually bathes the surface of the oral mucosa and maintains a moist, stable environment	Saliva is a relatively mobile fluid
	Compared to the secretions of the gastrointestinal tract, saliva contains less mucin, limited enzymatic activity and virtually no proteases	
Flexible membrane	Some membranes are less flexible than others (e.g. gums, hard palate)	Can cause delivery systems to dislodge from the mucosa
Structures (teeth, gums, tongue, cheek, and palate)	Provide a variety of sites for drug delivery	The taste receptors in the tongue can prevent the formulation of bitter drugs; taste masking is difficult since pleasant tastes increase salivation and drug swallowing
	Delivery systems or devices can be affixed to structures, including non-absorbing structures such as teeth	
pH	Saliva has a slightly acidic pH which is favourable for a wide range of drugs	
	pH can be modified easily at the site of administration	
Keratinized mucosa	Usually located in regions of the mouth that do not flex (gum, palate)	Provides an additional barrier to drug absorption
Non-keratinized mucosa	More permeable than keratinized mucosa (buccal, sublingual)	Tend to be in regions of the mouth that are flexible
Membrane thickness	Sublingual mucosa is relatively thin, therefore this region is good for the purpose of rapid drug absorption	Buccal mucosa is relatively thick and absorption may be too slow to be useful for drug delivery
Surface area	Generally sufficient to allow for drug absorption of drugs with appropriate physicochemical properties	Relatively small compared to other absorption sites of the body
Eating		Can cause dislodgment of delivery systems
Drinking		Drinking can cause excessive dissolution or erosion of the delivery system
		Hot or acidic fluids can change the rate of drug release, or alter the mucoadhesive properties of the dosage form

Table 2.3 (continued)

Aspect	Advantage	Disadvantage
Swallowing		Removal of drug and/or dosage form from the intended site of absorption
Mastication	Chewing can distribute drugs around the oral cavity, increasing the surface area for absorption. Useful property for chewing gum delivery systems	Chewing can cause the patient to bite into the delivery system

Table 2.4 Desirable drug physicochemical properties for formulation of an oral mucosal drug delivery system [3–6, 15]

Formulation considerations	Ideal limits
Aqueous solubility	> 1 mg/mL
Lipophilicity	10 < oil:water partition coefficient < 1000
Molecular weight	< 500 Da
Melting point	< 200°C
pH of saturated aqueous solution	pH 5–9
Required dose deliverable	< 10 mg/day
Irritation potential, which is the net effect of many physicochemical properties	No irritation to buccal tissue

In addition to these major pathways, other transport mechanisms (e.g. carrier-mediated transport) play a role in the transport of some drugs across the oral mucosa [14].

2.3.3 Influence of Drug Properties on Oral Mucosal Drug Delivery

The physicochemical properties of the drug play a crucial role in the design and formulation of an oral mucosal drug delivery system. It is of paramount importance that the physicochemical properties of the drug are characterized in order to allow for initial selection and subsequent formulation into an oral mucosal drug delivery system. The physicochemical properties of the drug that need to be known prior to its formulation into an oral mucosal drug delivery system are shown in Table 2.4.

2.3.4 Facilitation of Drug Effectiveness from an Oral Mucosal Drug Delivery System

Two factors influence the effectiveness of drug delivery from a delivery system designed for use in the oral cavity. The first is time of retention of the drug delivery

system in contact with the oral mucosa; the second is the permeation rate of the drug across the oral mucosa.

The ability to retain the drug delivery system in contact with the oral mucosa at a particular location can be achieved through the incorporation of carefully selected mucoadhesive polymers into the formulation. This results in the delivery system having an intimate contact with the oral mucosa for a prolonged time. When mucoadhesive polymers rapidly and securely interact with the mucin molecules, found on the surface of the oral mucosa, it results in intimate contact of the dosage form with the mucosa. The prolonged contact time allows for a longer duration for absorption of the drug. It also reduces the pathway for diffusion of released drug between the surface of the delivery system and the surface of the mucosa.

Increasing the permeability of the drug through the oral mucosa is another approach [16] used to assure therapeutic levels of a drug via the buccal route. This is commonly achieved through the use of a penetration enhancer in the formulation. Various chemicals have been used as permeation enhancers. These include surfactants, bile salts, fatty acids and non-surfactants (such as cyclodextrins, chitosan and Azones) [6,17,18,19–21].

Mucoadhesive polymers [22–24] and penetration enhancers used for oral mucosal delivery have been extensively reviewed by several authors in recent years [16,25] and readers are referred to these reviews for further information.

2.4 Oral Mucosal Drug Delivery Systems

A recently published review suggested that oral mucosal drug delivery systems are actively being conceptualized and invented, and significant time is being devoted in both academia and industry to research this route of drug delivery [7]. The same review highlights that there are less than 50 registered products available for buccal/sublingual delivery in the USA at its time of writing (2012) [26]. 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 past two decades and the products for oral mucosal drug delivery actually reaching the market [7]. A number of oral mucosal drug delivery systems such as tablets, lozenges, sprays, wafers, strips, films, etc. have been described in the literature [27–29]. Some of these are briefly reviewed below.

Abstral This is a sublingual tablet comprising a rapidly disintegrating, fast-acting formulation of fentanyl citrate. Abstral was the first approved fast-acting, rapidly disintegrating tablet formulation for breakthrough cancer pain in the USA (other formulations were non-disintegrating). The product is now marketed by ProS-trakan Ltd. across the principal European markets [30]. Abstral is formulated in six strengths: 100, 200, 300, 400, 600 and 800 µg, distinguishable by the shape of the tablet (round-, oval-, triangle-, diamond—“D”—and capsule-shaped, respectively) and by debossing on the tablet surface.

Actiq This product is a lozenge containing 200, 400, 600, 800, 1200 or 1600 µg of fentanyl citrate now marketed by Teva Pharmaceuticals Industries Ltd.'s Cephalon unit. It was the first product labelled for breakthrough cancer pain (1998). The lozenge is formulated into the shape of a lollipop. Thus, it can be described as a solid formulation (lozenge) on a plastic stick (an integral oromucosal applicator). The lozenge dissolves slowly in the mouth for absorption across the *buccal mucosa*. An Actiq lozenge is formulated as a white to off-white compressed powder drug matrix attached using edible glue to a fracture-resistant, radio-opaque plastic applicator, marked with the dosage strength. Its formulation includes dextrates (equivalent to approximately 2 g of glucose), sucrose (approximately 30 mg confectioner's sugar) and propylene glycol (part of the artificial berry flavour and imprinting ink) as excipients. Actiq should be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximizing the amount of mucosal exposure to the product. The Actiq lollipop should be sucked, not chewed, as absorption of fentanyl via the buccal mucosa is rapid in comparison with systemic absorption via the gastrointestinal tract. The patient should consume the lollipop over 15 min.

Aftach Nagai [31] was among the first to pioneer the bioadhesive tablet 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) [32].

Breakyl The first product to be approved in the European Union, using the Bio-Erodible MucoAdhesive (BEMA) drug delivery technology is Breakyl. It consists of a small, bioerodible polymer film for application to the buccal mucosal membranes (inner lining of the cheek) (BioDelivery Sciences International, Inc.) [33]. BEMA films were designed to rapidly deliver a drug dose across the mucous membranes for time-sensitive conditions, or to facilitate administration of drugs with poor oral absorption.

Buccastem This is a tablet formulation of prochlorperazine used for the treatment of nausea and vomiting, marketed by Alliance Pharmaceuticals Ltd. [34]. The tablet is placed in the buccal area where it releases the drug over a few hours. Each buccal tablet contains 3.0 mg prochlorperazine maleate. When the tablets are placed in the buccal cavity, they form a gel from which the prochlorperazine is released and absorbed. The plasma levels achieved at steady state on a dosage regimen of one buccal tablet twice daily are similar to those observed with the standard oral dosage of one 5 mg tablet taken three times daily. Its formulation contains compressible sugar, Povidone K30, xanthan gum, locust bean gum, talc, magnesium stearate and riboflavin sodium phosphate.

Buccolam This oral mucosal solution, containing 10 mg midazolam in 2 mL, is for paediatric use [35]. Buccolam (ViroPharma SPRL) is provided in a prefilled, age-specific dose formulation for administration to an area between the cheek and gum. It is a clear, colourless solution with a pH between 2.9 and 3.7. Its formulation contains sodium chloride, water for injections, hydrochloric acid for pH adjust-

ment and conversion of midazolam to the hydrochloride salt and sodium hydroxide (again for pH adjustment).

Epistatus This liquid buccal formulation of midazolam is available for the treatment of status epilepticus and serious tonic-clonic seizures in community settings. It is an unlicensed medicine made under Manufacturers Specials licence MS 123. Compared to its competitor, rectal diazepam, it provides a more convenient-to-use, and less embarrassing, option for the child.

Fentanyl Oralet This was the first Food and Drug Administration (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.

Fentora Effervescence is used in this buccal tablet to promote the absorption of fentanyl. It became the second fentanyl oral transmucosal dosage form to be commercially marketed (Teva Pharmaceuticals Industries Ltd.'s, Cephalon unit) with an indication for breakthrough cancer pain [36,37]. The effervescent delivery system exhibits a much higher bioavailability than the same dose of fentanyl from an Actiq lollipop. The tablet is placed in the buccal cavity (above a premolar, between the gum and the cheek) where it disintegrates over approximately 10 min, thereby releasing the drug. The fentanyl buccal tablet received approval from the European Commission in 2008 under the trade name, Effentora.

Intermezzo This is a sublingual tablet containing zolpidem tartrate that is available in two strengths (3.5 and 1.75 mg) for the indication of middle-of-the-night insomnia [38,39]. It is made by Transcept Pharmaceuticals Inc. of Point Richmond. The formulation is designed to enhance sublingual permeation. The product is unique in that females are recommended a lower dose.

Loramyc (Oravig) This mucoadhesive tablet containing 50 mg of miconazole is based on the Lauriad™ technology. The inactive ingredients are milk protein concentrate, hypromellose 2208, maize starch, lactose monohydrate, sodium laurylsulphate, magnesium stearate and talc. The tablet gradually becomes hydrated and sticks to the proteins of the mucous surface, and then releases the active pharmaceutical ingredient on a prolonged basis [40]. They are white to slightly yellow tablets with a rounded side and a flat side debossed with "L." Loramyc is applied to the upper gum just above the incisor tooth. The rounded side of the tablet should be applied to the upper gum by holding the tablet in place for 30 s with a slight pressure of the finger over the upper lip. With each application of the mucoadhesive tablet, the tablet should be applied to alternate sides of the upper gum.

MetControl A metformin medicinal chewing gum developed by Generex Biotechnology Corporation for the treatment of type 2 diabetes mellitus and obesity is available commercially [41]. The smaller dose of buccally administered drug is expected to reduce the gastrointestinal irritation and bloating caused by metformin.

Oral-lyn A liquid formulation of regular recombinant human insulin that is delivered to the buccal mucosa is available. It uses the RapidMist technology which supplies a fine mist of the formulation to the mouth. Insulin absorption is limited to the

mouth with no entry into the lungs. This technology uses the formation of micro-fine, thin membrane, mixed micelles made from the combination of insulin and specific absorption enhancers that encapsulate and protect the insulin molecules. Oral-lyn buccal insulin spray has been shown to produce a significant reduction of HbA1c compared with a control group, with no adverse events [42].

Sativex This is an oromucosal spray containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), medicines derived from cannabis, to be delivered to multiple sclerosis (MS) patients suffering from muscle spasticity [43]. It is a yellow/brown solution in a spray where each millilitre contains 38–44 and 35–42 mg, respectively, of two extracts from *Cannabis sativa* L., folium cum flore (*Cannabis* leaf and flower). The extracts are in the form of soft extracts, corresponding to 27 mg delta-9-tetrahydrocannabinol and 25 mg cannabidiol. It is recommended that the spray should be directed at different sites on the oromucosal surface each time the product is used.

Striant This buccal system is designed to adhere to the gum or inner cheek. It provides a novel treatment option for the 4–5million men who require testosterone replacement therapy for a deficiency or absence of endogenous testosterone associated with hypogonadism [44].

Subutex and Suboxone Tablets These are tablet formulations, made by Reckitt Benckiser Pharmaceuticals Inc. and contain buprenorphine for initiating treatment of opioid dependence. Subutex contains only buprenorphine hydrochloride. This formulation was developed as the initial product. The second medication, Suboxone contains naloxone to guard against misuse [45]. Subutex is available as 2 mg sublingual tablets. The tablet usually fully dissolves under the tongue within 5–10 min. It contains monohydrated lactose, mannitol, maize starch, Povidone K30, citric acid and sodium citrate as excipients. Suboxone tablet contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate) or 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate). Its excipients are similar to those listed under Subutex tablets.

Suboxone Film This is a fast-dissolving sublingual film containing buprenorphine and naloxone in which the PharmFilm® technology is utilized. This technology is a strip dosage form [46] claiming to be absorbed via the buccal or sublingual mucosa. In general, the thin strip dosage form 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 are less pleasant to use and the convenience of portability is compromised. Hence, a disadvantage of thin strips is that they have a low dose-loading capacity (no more than about 40 mg/strip at most). Suboxone films have replaced Suboxone tablets in order to better control misuse and accidental paediatric exposure. The individually packaged films are more difficult for children to open [47].

Subsys Available as a sublingually administered single-dose spray formulation of fentanyl in a novel delivery device, Subsys offers numerous benefits to patients who

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