Chapter Three

Drug Delivery to the Oral Cavity or Mouth

ANATOMY AND PHYSIOLOGY

The oral cavity

The oral cavity or mouth is the point of entry of food and air into the body and the mouth and lips are essential to humans to allow speech by modifying the passage of air. This structure is also referred to as the buccal cavity, but strictly speaking this should be confined to the inner cheek area. The mouth extends from the lips to the oropharynx at the rear and is divided into two regions: (a) the outer oral vestibule, which is bounded by the cheeks and lips, and (b) the interior oral vestibule, which is bounded by the dental maxillary and mandibular arches. The oral cavity proper is located between the dental arches on which the teeth are situated. It is partly filled by the tongue, a large muscle anchored to the floor of the mouth by the frenulum linguae (Figure 3.1). At the back of the oral cavity are large collections of lymphoid tissue forming the tonsils; small lymphoid nodules may occur in the mucosa of the soft palate. This tissue plays an important role in combating infection.

The palate

The palate is located in the roof of the mouth. It separates the nasal and oral cavities. It consists of an anterior hard palate of bone and, in mammals, a posterior soft palate that has no skeletal support and terminates in a fleshy, elongated projection called the uvula. The hard palate, which composes two-thirds of the total palate area, is a plate of bone covered by a moist, durable layer of mucous-membrane tissue, which secretes small amounts of mucus. This layer forms several ridges that help grip food while the tongue agitates it during chewing. The hard palate provides space for the tongue to move freely and supplies a rigid floor to the nasal cavity so that pressures within the mouth do not close off the nasal passage. The soft palate is composed of muscle and connective tissue, which give it both mobility and support. This palate is very flexible; when elevated for swallowing and sucking, it completely blocks and separates the nasal cavity and nasal portion of the pharynx from the mouth and the oral part of the pharynx. While elevated, the soft palate creates a vacuum in the oral cavity, which keeps food out of the respiratory tract.

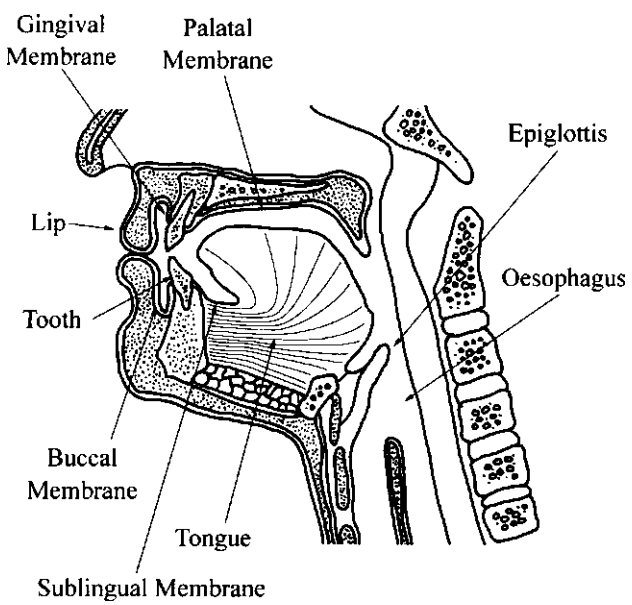

Figure 3.1 Cross section through the oral cavity

The tongue

In humans, the tongue aids in creating negative pressure within the oral cavity that enables sucking, and it is an important accessory organ in chewing, swallowing and speech. The tongue consists of a mass of interwoven, striated muscles interspersed with glands and fat and covered with mucous membrane. The ability of the tongue to touch the lips and teeth aids swallowing and speech. The top surface, or dorsum, contains numerous projections of the mucous membrane called papillae. They contain taste buds sensitive to food flavours and serous glands that secrete some of the fluid in saliva. The base, or upper rear portion, of the tongue has no papillae, but aggregated lymphatic tissue (lingual tonsils) and serous and mucus-secreting glands are present. The inferior, or under surface leads from the tip of the tongue to the floor of the mouth; its mucous membrane is smooth and purple in colour from the many blood vessels present. The root, the remainder of the underside that lies on the floor of the mouth contains bundles of nerves, arteries, and muscles that branch to the other tongue regions. Nerves from the tongue receive chemical stimulation from food in solution which gives the sensation of taste. There are four fundamental taste sensations: salt and sweet, the receptors for which are primarily located at the tip of the tongue, bitter at the base, and acid or sour along the borders. The flavour of a food comes from the combination of taste, smell, touch, texture or consistency, and temperature sensations.

The teeth

Teeth cut and grind food to facilitate digestion. A tooth consists of a crown and one or more roots. In humans, they are attached to the to the tooth-bearing bone of the jaws by a fibrous ligament called the periodontal ligament or membrane. The neck of the root is embedded in the fleshy gum tissue. Cementum is a thin covering to the root and serves as a medium for attachment of the fibres that hold the tooth to the surrounding tissue (periodontal membrane). Gum is attached to the alveolar bone and to the cementum by fibre bundles.

Caries, or tooth decay, is the most common disease of the teeth among humans. Tooth decay originates in the build-up of a yellowish film called plaque on teeth, which tends to harbour bacteria. The bacteria that live on plaque ferment the sugar and starchy-food debris found there into acids that destroy the tooth's enamel and dentine by removing the calcium and other minerals from them. Alkali production from urea by bacterial ureases in the oral cavity is thought to have a major impact on oral health and on the physiology and ecology of oral bacteria[1]. Another common dental disorder is inflammation of the gum, or gingivitis. It usually commences at or close to the gum margin, often between adjacent teeth. Pockets form between the gum and the adjacent teeth, sometimes penetrating deeply into the tissues. This leads to further infection, with inflammation and bleeding from the infected gums. A principal cause of gingivitis is the build-up of plaque on teeth, which causes irritation of the gums and thus leads to their inflammation and infection.

Organisation of the oral mucosa

The oral cavity and vestibule are entirely lined by relatively smooth mucous membranes containing numerous small glands (Figure 3.2). It is divided into a) the oral epithelium, b) the basement membrane, which connects the epithelium to the connective tissue, c) the lamina propria, which is underlying connective tissue and d) an area which contains loose fatty or glandular connective tissue and major blood vessels and nerves. It is often referred to as the muco-periostium. These tissues are laid over a layer of muscle or bone. To a certain extent, the structure of the oral mucosa resembles that of the skin.

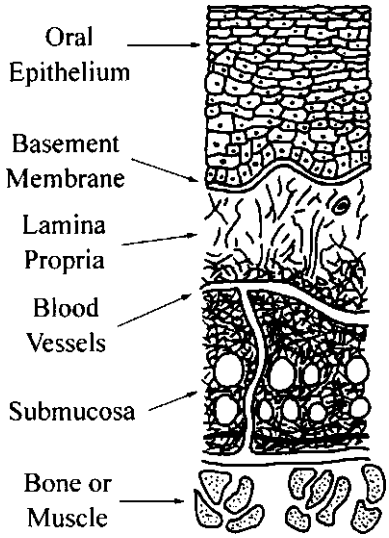

Figure 3.2 Cross section through the oral mucosa

The epithelial lining of the oral mucosa is composed of squamous cells with a characteristic layered structure formed by the process of cell maturation. The composition and thickness of this layer varies according to the tissue functions; the hard palate and tongue, for example, is composed of keratinized epithelium whilst the lining of the cheek is distensible and non-keratinized (Table 3.1). Keratinised tissue is dehydrated, tough and resistant to chemical damage and it covers approximately 50% of the surface. Non-keratinised tissue is more flexible and occupies about 30% of the surface area. The oral mucosa has a turnover time of 3–8 days.

Sebaceous glands are found in the mucosa of 60 to 75% of adults and are seen as pale yellow spots in the upper lip and buccal mucosa. The openings of minor salivary glands are evident in many areas. In general, the oral mucosa has a more concentrated network of vessels than is present in the skin. Almost all venous return from the oral mucosa enters the internal jugular vein. Lymphatic capillaries are also present in the lamina propria and arise as "blind" beginnings in the papillae.

Table 3.1 Characteristics of the mucosae found in the oral cavity

Tissue	Location	Thickness mm	Type
Gingival	Gums	0.2	Keratinized / nonpolar
Palatal	Roof of mouth	0.25	Keratinized / nonpolar
Buccal	Cheek Upper and lower lip	0.55	Nonkeratinized / polar
Sublingual	Frenulum Floor of mouth	0.15	Nonkeratinized / polar

Functions of the oral mucosa

The oral mucosa has similarities to both skin and intestinal mucosa. It has a protective role during the process of mastication, which exposes the mucosa to compression and shear forces. Areas such as the hard palate and attached gingiva have a horny surface to resist abrasion and are tightly bound to the underlying bone to resist shear forces. The cheek mucosae, on the other hand, are elastic to allow for distension.

The oral cavity contains the greatest variety of micro-organisms present within the human body. The entry into the body of these organisms and any potential toxic waste product is limited by the oral epithelium, which is not, as is often suggested, a highly permeable membrane.

The oral mucosa responds to the senses of pain, touch, and temperature in addition to its unique sense of taste. Some physiological processes are triggered by sensory input from the mouth, such as the initiation of swallowing, gagging and retching.

In some animals the oral mucosa is used to aid thermoregulation, for example, panting in the dog. The human skin possesses sweat glands and a more highly controlled peripheral vasculature, so this role is thought to be minimal, although in sleep, dehydration can result from prolonged breathing through the mouth.

Salivary secretion

Salivary glands

The major salivary glands are the parotid, submandibular (submaxillary) and sublingual glands (Figure 3.3). Minor salivary glands are situated in or immediately below the oral mucosa in the tongue, palate, lips, and cheeks. The major glands are situated some way from the oral cavity, but open into it by a long duct. The parotid salivary glands, the largest of the three, are located between the ear and ascending branch of the lower jaw. Each gland is enclosed in a tissue capsule and is composed of fat tissue and secretory cells and the major duct (Stensen's duct) opens near the second upper molar. The second pair, the submaxillary

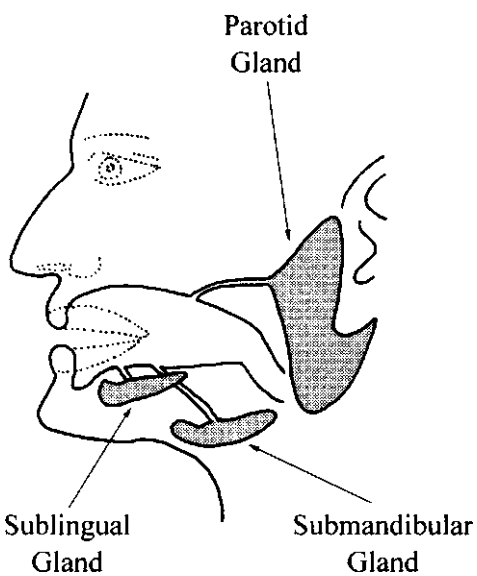

Figure 3.3 Position of the salivary glands

glands, is located along the side of the lower jawbone. The major duct of each (Wharton's duct) opens into the floor of the mouth at the junction where the front of the tongue meets the mouth's floor. A capsule of tissue also surrounds each of these glands. The third pair, the sublingual glands, is situated beneath the mucous membrane of the floor of the mouth, near the chin region. They are not covered by a capsule and are therefore more dispersed throughout the surrounding tissue. They have many ducts (Rivinus's ducts) that empty near the junction of the tongue and the mouth's floor; several unite to form Bartholin's duct which empties into or near the submaxillary duct. The parotid and submaxillary glands produce watery secretion, while the buccal and sublingual glands produce mainly viscous saliva.

Saliva

One to two litres of fluid are excreted daily into the human mouth and there is a continuous, low basal secretion of 0.5 $ml.min^{-1}$ which will rapidly increase to more than 7 $ml.min^{-1}$ by the thought, smell or taste of food. Control over salivary secretion is exerted primarily via the parasympathetic system. Small amounts of saliva are continually being secreted into the mouth, but the presence of food, or even the smell or thought of it, will rapidly increase saliva flow. Saliva is viscous, colourless and opalescent, hypotonic compared to plasma (between 110 and 220 milliOsmoles per litre), with a specific gravity of about 1003. The pH varies between 7.4 to 6.2 (low to high rates of flow), but the action of bacteria on sugar can reduce the pH to between 3 and 4 around the teeth.

Saliva can be detected in the oral cavity soon after birth. Salivary secretion increases up to the age of 3 to 5 years, but then sharply declines, reaching a steady state by the age of 8 years. In adult females, the flow rate of saliva is somewhat lower than in males[2].

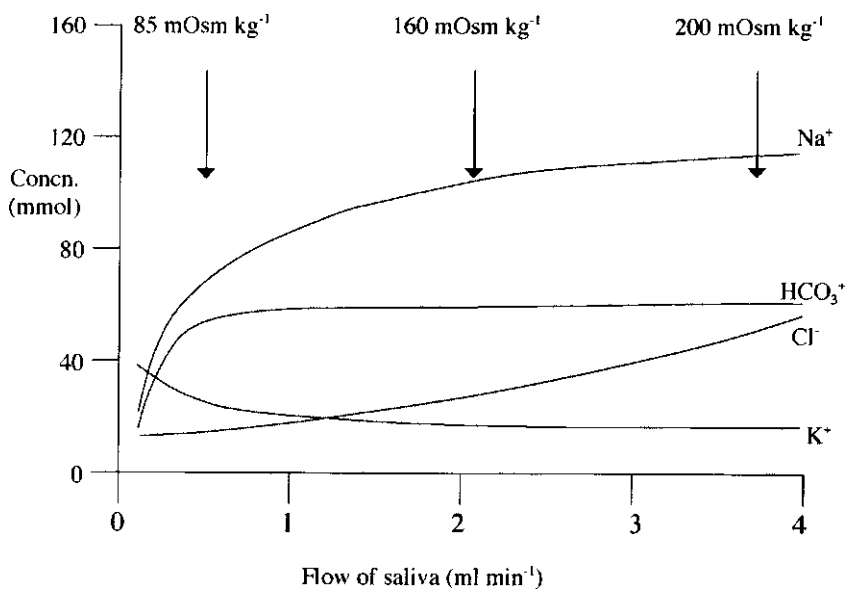

Figure 3.4 Influence of flow on saliva composition

Saliva is primarily composed of water, mucus, proteins, mineral salts, and amylase[3]. As it circulates in the mouth cavity it picks up food debris, bacterial cells, and white blood cells. The composition of saliva depends upon the rate at which the different cell types contribute to the final secretion. The two types of secretion are mucous secretion, which is thick due to a glycoprotein called mucin, and watery secretion which contains salivary amylase. The major ions are Na^+, K^+, Cl^- and HCO_3^-. In the ducts of the salivary glands, sodium and chloride are reabsorbed, but potassium and bicarbonate are secreted (Figure 3.4) and hence the electrolyte balance is altered depending upon the rate of flow of saliva.

Apart from the enzyme a-amylase, ptyalin is also present. This enzyme begins to hydrolyse polysaccharides such as glycogen and starch to smaller saccharides. The enzyme acts at an optimum pH of 6.9, but is stable within the range 4 to 11 and hence it will continue to act until the food is acidified by gastric acid. The time of contact in the mouth is too short for digestion to occur but the enzyme may prevent accumulation of starchy material in the gaps between teeth. Lingual lipase is responsible for hydrolysis of triglycerides. It is extremely hydrophobic and its digestive action continues in the stomach. A variety of esterases, mainly carboxylesterases are also present in the saliva and these may reduce the concentration of ester prodrugs or drugs containing susceptible ester groups[4].

Saliva lubricates and moistens the inside of the mouth to help with speech and to change food into a liquid or semisolid mass that can be tasted and swallowed more easily. The salivary film thickness is estimated to be between 0.07 and 0.10 mm[5]. It also helps to control the body's water balance; if water is lacking, the salivary glands become dehydrated, leaving the mouth dry producing a sensation of thirst thus stimulating the need to drink. The flow of saliva helps to wash away the bacteria and the food particles which act as their nutrient, into the acidic environment of the stomach where they are digested. Saliva also contains thiocyanate, and protein antibodies and lysozyme which destroy bacteria. In the absence of saliva, oral ulcerations occur and dental caries becomes extremely prevalent. This condition, xerostomia, can be treated with artificial saliva formulations, which are based on materials such as hydroxypropylmethylcellulose and more recently, pig gastric mucin.

MIGRATION AND CLEARANCE OF SUBSTANCES FROM THE ORAL CAVITY

Powdered charcoal placed under the tongue spreads through the oral cavity within a few minutes[6], but regional differences exist in the deposition, distribution and clearance of drugs which are dissolved in saliva[7]. This is of great importance if local treatment of the entire mucosa is required or the drug is absorbed preferentially from certain sites. Studying the pattern of fluoride concentration in the mouth arising from a slowly dissolving fluoride tablet revealed that when the tablet was placed in the lower mandibular sulcus, fluoride concentrations increased markedly in the region of the tablet, but there was no appreciable increase in salivary levels[8]. Relatively little had migrated to the opposite side of the mouth suggesting that the lower mandibular sulci are quite isolated from the remainder of the mouth. However, when the tablet was placed in the upper sulcus the fluoride migrated some distance from the site of administration. Glucose behaves in a similar fashion[9]. The pattern of fluoride distribution and the fluoride concentration are fairly consistent for any one subject, but a 20-fold intrasubject variation was observed. It is believed that the site specific differences are due to saliva movement and dilution of the test substance rather than the nature of the substance. The thickness of the salivary film will vary from place to place depending upon the proximity to the ducts of the major and minor salivary glands, separation of mucosal layers during speaking and mouth breathing.

ABSORPTION OF DRUGS ACROSS THE ORAL MUCOSA

The oral cavity is the point of entry for oral drug formulations but usually their contact with the oral mucosa is brief. In order to take advantage of some of the properties of the oral mucosa or to locally treat the mucosa, delivery systems have been designed to prolong residence in this area. The total surface area available for drug absorption is quite limited, being only approximately 100 cm^2.

Absorption of drugs through the buccal mucosa was first described by Sobrero in 1847 who noted systemic effects produced by nitroglycerin after administration to the oral mucosa[10]. The lingual route of administration became established in clinical practice in 1897 when William Murrell introduced nitroglycerin drops for the treatment of angina pectoris. Subsequently, nitroglycerin was formulated in tablets for sublingual use and was renamed glyceryl trinitrate.

The blood supply from the buccal mucosa and anal sphincter, unlike the remainder of the gastrointestinal tract, does not drain into the hepatic portal vein, since these peripheral areas are not specialised for the absorption of nutrients. Drugs which are absorbed through the oral mucosa enter the systemic circulation directly via the jugular vein, thereby initially avoiding passage through the liver where they might otherwise be metabolized. Drugs which are swallowed in the saliva do not avoid first pass metabolism and will be subjected to degradation by digestive juices.

The oral cavity is rich in blood vessels and lymphatics, so a rapid onset of action and high blood levels of drug are obtained quickly. In many cases buccal dose forms can result in the same bioavailability as intravenous formulations, without need for aseptic preparations. Finally, they share with transdermal systems the advantage that treatment can be rapidly stopped by removing the dose form, although the buccal epithelium can act as a reservoir for administered drug after the delivery system has been removed. Ideally the plasma concentration versus time profile should resemble a square wave, similar to that seen after skin application of a glyceryl trinitrate patch, but this is not always achievable.

In order to be absorbed orally, the drug must first dissolve in the saliva. Extremely hydrophobic materials (those with partition coefficients greater than approximately 2000) will not dissolve well and are likely to be swallowed intact unless a specialized delivery system is used to present them to the mucosa. Saliva containing dissolved drug is constantly being swallowed, and this process competes with buccal absorption. As described in Chapter 1, a balance must be found between good dissolution (implying a large ionized fraction of drug) and a large unionised fraction of drug (implying poor solubility but good absorption). A partition coefficient range of 40–2000 has been found to be optimal for drugs to be used sublingually. The importance of partition can be seen in the absorption of p-substituted phenylacetic acids, which have approximately the same pKa. The buccal absorption at pH 6 is, (in order of increasing hydrophobicity): hydrogen—1%, nitro—1%, methoxy—3%, methyl—7%, ethyl—10%, t-butyl—25%, n-butyl—34% n-pentyl—49%, cyclohexyl—44% and n-hexyl—61%[11].

Disadvantages of oral mucosal delivery

Not surprisingly, there are disadvantages to this route of administration. The buccal cavity, like the entire alimentary canal, behaves as a lipoidal barrier to the passage of drugs. Active transport, pinocytosis, and passage through aqueous pores play only insignificant roles in moving drugs across the oral mucosa, hence the majority of absorption is passive, and only small lipophilic molecules are well absorbed. Polar drugs, for example those which are ionized at the pH of the mouth (6.2–7.4), are poorly absorbed. Little intercellular absorption is possible across the cuboid squamous pavement epithelium of the oral cavity.

However, some amino acids such as glutamic acid and lysine[12] and some vitamins such as L-ascorbic acid[13], nicotinic acid[14] and thiamine[15] are reported to be transported via a carrier-mediated process.

Another major problem is that the dose form must be kept in place while absorption is occurring, since excessive salivary flow may wash it away. The total area for absorption is low compared to other routes, being in the region of 100–170 cm^2[5]. The taste of the drug must be bland, otherwise it will not be acceptable. The drug must also be non-irritant, and it should not discolour or erode teeth. This may be partly overcome by using a drug delivery system which has a unidirectional drug outflow which is placed against the mucosa. However, these systems do have the potential for lateral diffusion and back partitioning of the drug into the oral cavity.

Effect of position on drug delivery

Within the oral cavity, delivery of drugs can be classified into four categories: (i) sublingual delivery in which the dosage form is placed on the floor of the mouth, under the tongue, (ii) buccal delivery, in which the formulation is positioned against the mucous membranes lining the cheeks, (iii) local oropharyngeal delivery to treat mouth and throat and (iv) periodontal delivery, to treat below the gum margin. Variations in epithelia thickness and composition will undoubtedly affect drug absorption. The permeability of the oral mucosa has been reviewed by Squier and Johnson[16]. The usual test of buccal absorption measures the average value of penetration of the drug through all the different regions of the oral mucosa, even though it is likely that regional differences in absorption occur. It has been suggested that drug absorption through the sublingual mucosa is more effective than through the buccal mucosa, even though both these regions are non-keratinized. The sublingual epithelium is, however, thinner and immersed in saliva, both of which will aid drug absorption (Figure 3.5).

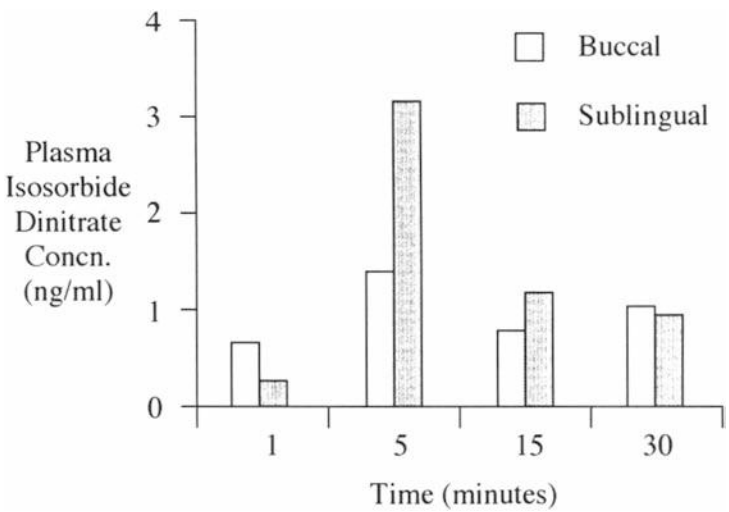

Figure 3.5 Comparison of isosorbide dinitrate absorption when drug is presented by the buccal and sublingual route

The rate of dissolution of the formulation may be position dependent, due to variations in its proximity to the major salivary gland and the water content of the saliva produced. The sublingual route is not suitable for the production of extended plasma concentration-time profiles, since absorption is completed quite quickly as the epithelium in the area is very thin (approximately 100 μm). This rapid absorption can lead to high peak plasma concentrations which may be overcome by delivering the drug to the thicker buccal mucosa which slows absorption. The metabolic activity of the oral mucosa and that of the resident population of bacteria can alter or degrade drugs[17].

The barrier function of the surface layers of the buccal epithelium depends upon the intercellular lipid composition. Epithelia which contain polar lipids (Table 3.1), notably cholesterol sulphate and glucosyl ceramides, are considerably more permeable to water than keratinized epithelia[18–20]. Intracellular lamellae, composed of chemically unreactive lipids, have been described in human buccal mucosa, and may be relevant to drug permeability[21].

During normal activities such as eating and drinking, the humidity and temperature in the oral cavity will be highly variable. The tongue is a highly sensitive organ and hence any device placed in the oral cavity will have to withstand being probed and explored by it, a process which the average patient will perform almost unconsciously. The sublingual area moves extensively during eating, drinking and speaking, so attachment of a delivery device to this region is likely to be impossible[22].

Intercellular junctions do not appear to affect the permeability of these tissues and it is possible that the presence of the intercellular barrier is not due to the distribution of the keratinized and non-keratinized layers, but rather to the presence of membrane-coating granules[16]. Membrane coating-granules are spherical or oval organelles, about 100–300 nm in diameter which are found in many stratified epithelia. These granules usually appear in the cells of the stratified spinosum in keratinized epithelia. As differentiation proceeds, they are discharged into the intercellular spaces by exocytosis. Membrane coating granules in keratinized epithelia have a structure of parallel lamination, whilst those in non-keratinized epithelia do not, but have an enclosed trilaminar membrane with finely granular contents which aggregate centrally. These organelles are absent from junctional epithelia and at the gingival margin, the areas of highest permeability. The barrier which the granules produce exists in the outermost 200μm of the superficial layer.

Two tracers which differ in size have been used to study the effective barrier produced by membrane coating granules. These are horseradish peroxidase (m. w. 40,000 Dalton, 5–6 nm in size) and colloidal lanthanum (2 nm in size) which are both hydrophilic and hence would be confined to aqueous pathways[23]. When applied topically these tracers only penetrated the first three cell layers, but when introduced subepithelially, they extended through the intercellular spaces into the basal cell layers of the mucosal epithelium. In both keratinized and non-keratinized epithelia, the limit of penetration was related to the presence of the membrane-coating granules, implying that they cause a major barrier to penetration.

Gingival penetration

The gingival sulcus (Figure 3.6) is lined on its external surface by oral sulcular epithelium, which is continuous with the oral epithelium, but it is non-keratinized and has similar permeability to the oral epithelium. However, the "leakiest" area of the oral mucosa is the junctional epithelium in the gingival sulcus. This area has been studied extensively with respect to inflammatory periodontal disease. It is well documented that enzymes, toxins and antigens from plaque enter into the local tissue through this route and produce an immune inflammatory response in the tissue. Radioisotope and fluorescent compounds injected systemically can be detected at the surface. In healthy people, the sulcus is shallow

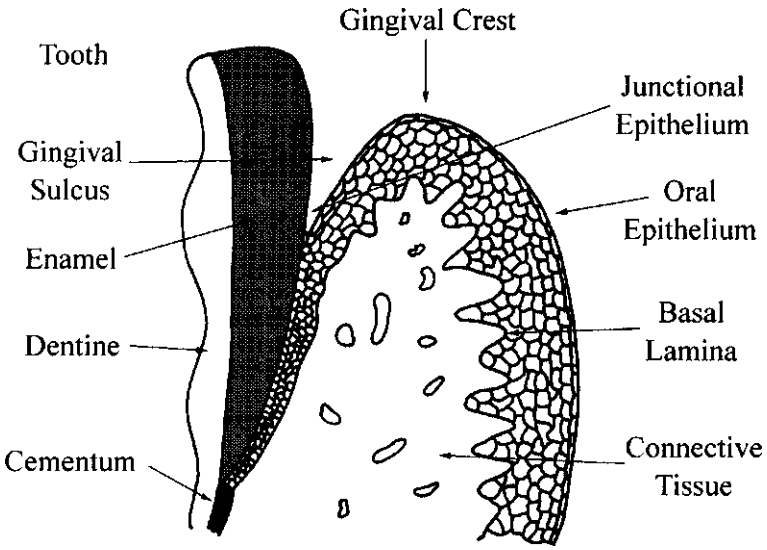

Figure 3.6 The gingival margin

or non-existent, and its base is formed by junctional epithelium, which extends from the base of the sulcus. The intercellular spaces in the junction epithelium are considerably larger than in either the oral sulcular epithelium or the oral epithelium, and desmosome attachment is four times less common. The sulcus produces a fluid which is composed of an inflammatory exudate[24]. Mild mechanical agitation of the surface of the sulcular epithelium increases the flow of gingival fluid, and it is believed that no fluid flow occurs if the tissue is undisturbed, both in healthy and inflamed states.

Studies which have been carried out to examine the penetration of materials into the body via this route have rarely distinguished between junctional epithelium and oral sulcular epithelium. In addition many animals show differences in the way the epithelium is attached to the tooth in the sulcular region. Substances which have been claimed at various times to penetrate the sulcular epithelium are albumin, endotoxins, thymidine, histamine and horseradish peroxidase, which indicates a permeability of substances up to a molecular weight of 1 million[16]. Particulate material such as polystyrene microspheres with a 1–3 μm range of diameters have been reported to penetrate the epithelium[25]. It is possible that substances entering the gingiva do so through the intercellular spaces[26 27]. Topically applied peroxidase was found in the intercellular spaces after 10 minutes and application of hyaluronidase, which increases intercellular space, causes increased tracer uptake[28].

Gingival disease and ageing are likely to influence drug absorption through the buccal cavity, since the gum margin may recede or become inflamed. This may allow more access to the underlying connective tissues which have little barrier function to small molecules.

Improving penetration through the mucosa

There are three methods by which penetration of compounds through the oral mucosa can be achieved:

a) increasing the metabolic stability of the drug either by the use of pro-drugs or co-administration of enzyme inhibitors. For example, ketobemidone absorption was greatly increased when the phenolic hydroxyl group of the drug was derivatised into a carboxylic acid or carbonate ester[29]. This improved lipophilicity and resistance to saliva catalysed hydrolysis.

b) penetration enhancers, including chelators such as ethylenediaminepentaacetic acid or salicylates, surfactants (e.g sodium lauryl sulphate), bile salts (e.g sodium deoxycholate), fatty acids (e.g. oleic acid) and membrane fluidizers (e.g. Azone®).

c) physical enhancement, e.g. stripping layers from the epithelium using an adhesive strip, scraping the mucosa, or the application of an electric field across the epithelium (iontophoresis, see Chapter 8).

The use of penetration enhancers may be necessary to achieve adequate absorption of large molecules. However, their action is non-specific and care must be taken to ensure that toxins and bacteria are not allowed to enter the body in addition to drug. Currently no marketed buccal or sublingual products contain excipients registered as absorption enhancers.

MEASUREMENT OF ORAL MUCOSAL DRUG ABSORPTION

The original buccal absorption test was introduced by Beckett and Triggs in 1967[30]. An oral solution of the drug is held in the mouth without swallowing. After a measured period, the mouth is emptied and rinsed, and the amount of unabsorbed drug remaining is assayed. This method has several disadvantages, primarily that an absorption-time profile must be built up from several separate experiments. The drug concentration also changes due to salivary secretion[31] and swallowing; this latter can be compensated by using a non-absorbed internal marker[32]. More recently Tucker[33] has described a modification of the method which uses continuous oral sampling so that repeated experiments are not necessary. All these procedures suffer from the drawback that only absorption from the whole oral epithelia can be measured, and if the absorption is low, the precision of the method is poor.

To measure the absorption of drug from a specific region, a small filter paper disc soaked in drug can be applied to the mucosa. This technique has been used to measure the uptake or loss of water, sodium and potassium ions[34]. A more elegant method of measuring drug absorption from the various regions is a chamber through which drug solution can be circulated which can be applied to various regions of the mucosa[35]. This has the advantage that both plasma levels and effluent from the chamber can be analysed for drug content.

DOSAGE FORMS FOR THE ORAL CAVITY

Creams and ointments cannot be used successfully in the oral cavity since they will not adhere well and may be washed away by saliva, although the original mucosal delivery system Orabase® (E.R.Squibb and Sons Inc.) consisted of finely ground pectin, gelatin and sodium carboxymethylcellulose dispersed in a poly (ethylene) and mineral oil gel base. Generally, oral drug delivery devices have been adapted from traditional technology, for example tablets, but these do not adequately address the problems unique to the mouth. Formulations which have been specifically designed for oral delivery include gums, fast-dissolving dosage forms and mucoadhesive patches.

It is important that neither the drug nor the excipients stimulate saliva secretion since this will increase the amount of drug swallowed. Taste, irritancy and texture problems may discourage patients from taking dosage forms which are designed to reside in the oral cavity. In order to enhance patient compliance, the dosage form has to be

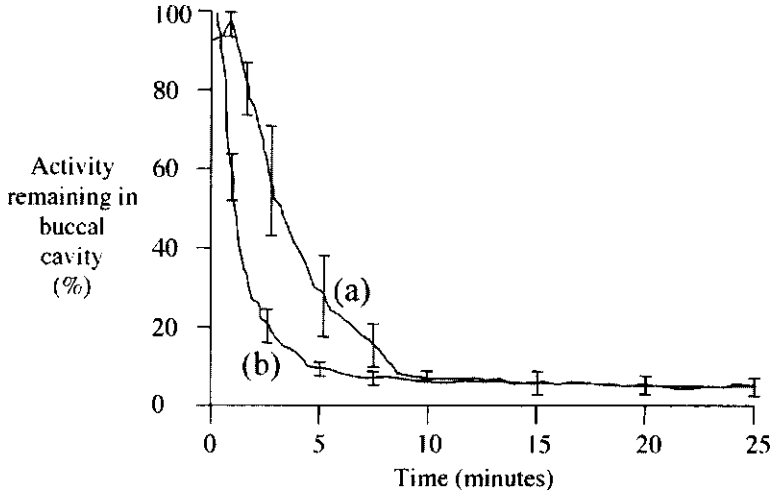

Figure 3.7 Release of a radiolabelled marker from a chewable formulations when (a) sucked and (b) chewed

unobtrusive and pleasant to take: a maximum dimension might be no larger than 3 cm^2. Some formulations are keratinolytic and hence cannot be placed over the same site without the risk of ulceration.

Chewable formulations

Chewing gum was first patented in 1869[36] and medicated chewing gum containing aspirin (Aspergum®) was marketed in the USA in 1924. It was the discovery that smokers self-titrate the amount of nicotine which they are absorbing which led to the development of a nicotine gum to help people trying to withdraw from the habit. In theory the gum could be chewed until the correct amount of nicotine was absorbed, then the formulation could be discarded. It has been of some value as a tobacco substitute for people attempting to give up smoking[37].

Patients who have difficulty in swallowing tablets or capsules may prefer chewable systems, which also have the great advantage that they can be taken without water. The most important physiological variable which will markedly affect the release characteristics of a drug is whether a person sucks or chews the formulation since systems designed to be chewed will invariably be sucked and vice versa by a proportion of patients (Figure 3.7). The abuse potential of narcotic drugs is reduced in this type of formulation since it is much harder to extract the active ingredient from the base for subsequent intravenous administration.

The release of a drug from chewing gum is dependent upon its water solubility. Water-soluble substances are released rapidly and completely from chewing gum but it is possible to retard and extend their release. Slightly water-soluble drugs are released slowly and incompletely from chewing gum and require special formulation techniques to produce a satisfactory release profile[38]. The release of ^{99m}Tc-HIDA, a hydrophobic marker, was prolonged from a chewing gum compared to a sublingual tablet or lozenge[39]. Gums can be used to deliver drugs for the treatment of dental health and antifungal therapy e.g. nystatin[40] and miconazole[41]. The absorption of some substances such as vitamin C can be increased

when administered in a gum compared to a conventional tablet[42]. Recently, mucin containing chewing gum has been used in the treatment of dry mouth[43].

Chewable formulations are used for the delivery of antacids where the flavouring agents give the sensation of relief from indigestion. Chewing antacid tablets prolongs the effect when compared to liquid antacids. Antacid tablets will react more slowly with gastric acid than liquids, even when thoroughly chewed, since the particle size will still be greater[44], but mixing the tablets with saliva also contributes to the prolonged duration of effect[45].

Fast-dissolving dosage forms

Fast dissolving dose forms for analgesics are well established as convenient systems for patient dosing, e.g. Solmin® (Reckitt and Colman Pharmaceuticals). These are solid dose forms which can be taken without water since they are designed to disperse on the tongue. They are also potentially useful where swallowing is difficult or oesophageal clearance is impaired.

Recently a new type of dosage form, Zydis™ (Scherer DDS), based on a freeze-dried mixture of drug and fast-dissolving excipients has been introduced to deliver sedative drugs such as benzodiazepines. Incorporation of ^{99m}Tc labelled micronised "Amberlite" CG400 resin during manufacture enabled the deposition and clearance of these formulations to be followed by gamma scintigraphy[46]. Two marker loadings were used, 2.5 mg and 10 mg, and the effect of incorporating the salivary stimulants talin and saccharin, and citrate, was investigated. Buccal clearance of the formulation containing the 10 mg resin was significantly faster than that containing 2.5 mg resin (Figure 3.8); however, calculation of the total activity remaining after dissolution showed that the amount remaining on the tongue was approximately 1 mg in each case. This probably represents the amount of resin

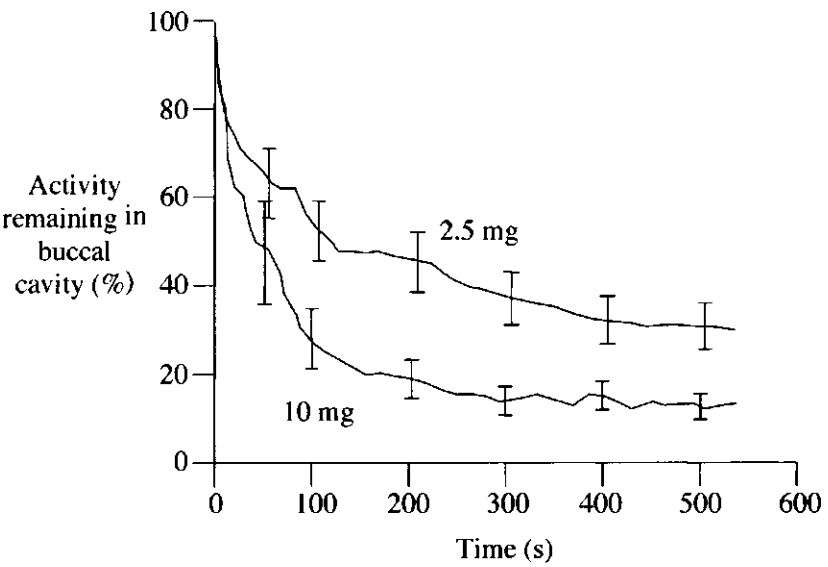

Figure 3.8 Clearance of a micronised resin from a Zydis™ formulation demonstrating trapping of resin between papillae on the tonge (mean clearance±sd)

trapped within the papillae of the tongue. There was little spread of the formulation laterally in the buccal cavity. Surprisingly, incorporation of salivary stimulants made little difference to the rate of dissolution of the formulation. Salivary stimulants increase the output of the submandibular and sublingual salivary glands, which discharge watery secretions onto the floor of the mouth, wetting the side of the tongue and cheek surfaces. The posterior third of the tongue surface contains mucus glands, but the quantity of secretion is relatively small. Thus increased salivary flow may not result in a more aqueous phase available for dissolution of the dosage form from the tongue surface. Delivery of drugs from a fast-dissolving formulation would not be expected to avoid first-pass metabolism since the unit disintegrates rapidly and the drug would be swallowed.

Bioadhesive dosage forms

Bioadhesion is a process which occurs when two materials, at least one of which is biological, are held together by interfacial forces. In pharmaceutics, bioadhesion is typically between an artificial material e.g. a polymer and/or a copolymer and a biological substrate. Where the biological substrate is covered with a mucus layer, the term "mucoadhesion" is used. It is described as a two-step process: first is the contact between two surfaces and second the formation of secondary bonds due to non-covalent bonding.

Many polymers can potentially be used in bioadhesive systems, including both water soluble and insoluble hydrocolloids, ionic and non-ionic and hydrogels. Appropriate materials for buccal delivery systems have to be mucoadhesive, have a sustained-release property and good feel in the mouth[47]. Bioadhesives have been formulated into tablets (e.g. Susadrin® (Pharmax Ltd.) which contains nitroglycerin[48]); gels and patches. Adhesive patches appear to be the most widely studied systems for buccal drug delivery. Patches vary

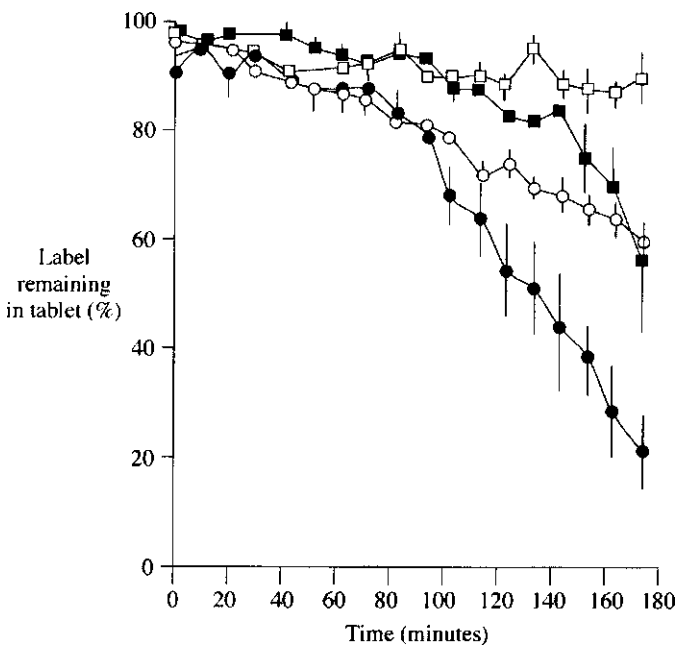

Figure 3.9 Inter- and intrasubject variation in the rates of release of a water soluble marker from a buccal mucoadhesive tablet

in design and range from simple credible systems, through non-erodible disks to laminated systems. Sizes vary from 1 to 15 cm^2, but smaller patches are much more comfortable. Patches will release drug both against the mucosa and into the oral cavity unless a backing layer is used to prevent release on the external face of the patch. Laminated systems permit local alteration of pH and inclusion of permeation enhancers which can markedly increase transport of drug. The use of the covered system removes luminal influences, such as saliva, mucus and enzymes, the presence of intercellular lipids, hence the mucosal thickness and the blood supply become rate limiting. The residence time of a bioadhesive system within the buccal cavity will depend on a variety of factors such as the strength of the mucoadhesive bond, the relative flexibility of both the system and the mucosa onto which it is adhered and the salivary flow. Hydrogels are currently being investigated extensively as bioadhesive vehicles for buccal drug delivery. They are swellable hydrophilic matrices that release a drug through the spaces in the polymer network by dissolution and disintegration.

Gamma scintigraphy was used to study the rate of release of ^{99m}Tc DTPA[49] from a buccal bioadhesive tablet (Figure 3.9). The tablet was designed to deliver glyceryl trinitrate and was based on a matrix of modified hydroxypropylmethylcellulose. The surface of the tablet quickly gels which serves both to anchor the tablet in position and to control the rate of diffusion of the drug[48]. The tablets are friable and the gel layer breaks on removal, and the in situ dissolution can be measured by gamma scintigraphy without disturbing the tablet. When the tablet was placed in the upper buccal pouch it was noted that between subjects there were marked differences in the rates of release, whereas within an individual measured on four occasions, the variation was quite small. This did not appear to be due to differences in saliva flow rate and the rate of dissolution, but interestingly may correlate with the extent to which the subject talked during the experiment. Articulation of the cheek surfaces during speech would increase the erosion of the tablet surface and hence the rate of release of the marker or drug into the buccal cavity. Drinking hot coffee or chewing gum did not affect the rate of release of marker. In general, when the tablet was placed behind the front incisors the rate of release of the marker was faster than when it was placed in the buccal cavity. The path of saliva flow in the human mouth can be monitored by measuring the distribution of charcoal particles placed at various locations in the mouth[6]. When the particles were placed under the tongue, the whole mouth became covered within 1 to 3 minutes, whereas administration to the lower right or left buccal vestibule covered that side of the tongue only. Hence, it is possible that salivary flow was responsible for the different rates of dissolution observed for the tablet.

Descriptions of a "semi-topical" buccal/gingival delivery system appeared in the literature about 12 years ago[50]. Lidocaine was delivered in an oral mucoadhesive tablet for the relief of toothache, or prostaglandin PGF2a into a gingival plaster for orthodontic tooth removal. Gingival absorption of lidocaine was poor due to the relatively low pH caused by the presence of carbopol-934, and more lipophilic derivatives such as dibucaine may be more suitable drug candidates. Studies in monkeys showed good results with the prostaglandin and limited clinical tests showed accelerated orthodontic tooth removal in 70% of patients studied.

Cydot™ (3M) is a flexible, mucoadhesive non-eroding disk which is placed on the gum. It has been used to deliver buprenorphene to volunteers and it is reported to remain in place for up to 17 hours regardless of food and drink consumed. The OTS (oral transmucosal system, TheraTech) is another commercially available device which has been used to deliver glucagon-like insulintropic peptide.

Dental systems

The use of antimicrobial agents in the treatment of chronic periodontal disease has utilised a variety of novel vehicles including hollow fibers, polymers (especially methacrylates) and oil-based vehicles to achieve sustained delivery of chlorhexidine, metronidazole and tetracycline. These materials are placed in the socket prior to occlusion with a dental appliance or wound dressing.

A controlled release compact containing tetracycline has been developed for treatment of severe forms of the diseases such as gingivitis, acute necrotising gingivitis, periodontitis and periodontosis[51]. The compacts (5 mm in diameter) were bonded to an upper molar and designed to release drug over a period of 10 days. The tetracycline reduced the quantity of plaque and gingival inflammation produced by the bacterial toxins around the gum margin. It is possible that similar systems can be developed to take advantage of the "leakiest" part of the buccal mucosa, the junctional epithelium.

A range of inflammatory, atrophic and ulcerative conditions occur in the mouth which justify the local application of corticosteroids[52]. The effect of the steroid reduces chemo-attractants which in turn reduces the migration of white cells and prevents the increased permeability of small vessels at the site of damage. The use of mucoadhesive patches promotes transmucosal absorption and extends the duration of effective administration. Mucoadhesive tablets based on a mixture of hydroxypropylcellulose and carbopol have been used for the delivery of triamcinolone[53]. Following application to the mucosa, the formulation draws in water which helps promote adhesion to the lesions and more effective treatment. Restricting the distribution of the steroid may also be advantageous since it is known that the use of topical aerosol sprays in the mouth may induce fungal infection.

DRUGS ADMINISTERED VIA THE ORAL MUCOSA

Nitrates

The largest number of commercially available products for buccal and sublingual delivery are for organic nitrates (nitroglycerin (GTN), isosorbide dinitrate)[54–58]. GTN was rapidly and more effectively absorbed (30–60 s) from 2.5–5 mg buccal doses compared to a 10 mg transdermal patch. It was shown to be effective in prolonging the time to angina pectoris during exercise after a single dose, the effect lasting about five hours. Less convincing was its beneficial effect on heart failure in elderly patients in an open study over a minimum of fourteen days. Long-term therapy with buccal or transdermal glyceryl trinitrate may be associated with tolerance to drug action caused by sustained high plasma concentrations. Buccal nitroglycerin is reported to be a better prophylactic in the treatment of angina pectoris than sublingual nitroglycerin due to its longer duration of action, whereas both routes are comparable in the treatment of acute attacks[58].

Steroids

Steroids such as deoxycorticosterone are absorbed through the oral mucosa, but a threefold increase in dosage over intramuscular injections is required[59]. Testosterone and methyltestosterone are more efficiently absorbed when delivered buccally than by the peroral route[60 61]. Methyl testosterone for treating hypogonadism and delayed puberty is available commercially in devices which utilise this route for delivery. A range of inflammatory, atrophic and ulcerative conditions occur in the mouth for which topical treatment of corticosteroids is indicated[62].

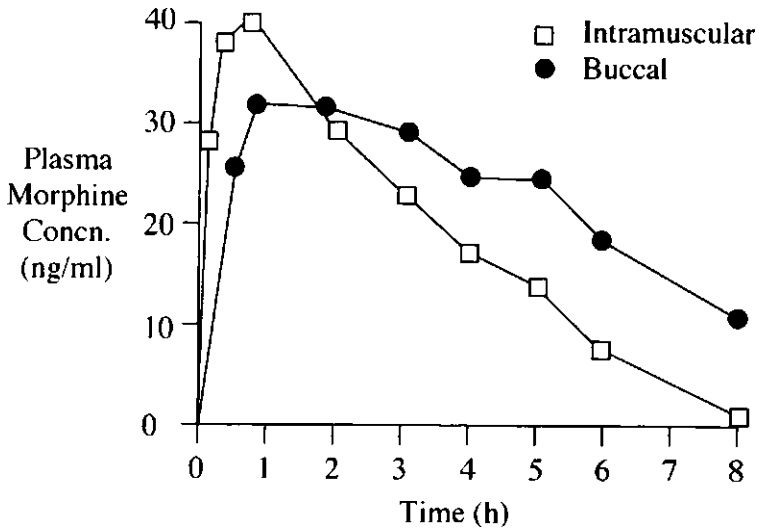

Figure 3.10 Plasma morphine concentration after intramuscular and buccal administration

Analgesics

Opioids (morphine, pethidine) are well absorbed with systemic availability and plasma concentrations which are similar to, or even higher than, that after intramuscular administration[63] (Figure 3.10). The reduction in post operative pain is comparable from both routes of administration[64]. Buccal morphine was reported not to be as effective as intramuscular morphine in relieving preoperative anxiety and wakefulness but this may have been produced by the lower bioavailability of the drug from the buccal dose form used[65 66]. A later study demonstrated that intramuscular administration of morphine produced an 8 fold increase in plasma levels compared to buccal administration. Buprenorphine is available as a sublingual commercial product for the treatment of analgesia.

Antibiotics

The oral cavity contains a diversity of microorganisms and over 300 different species of bacteria have been identified in the mouth. The density of microorganisms is high and saliva, which derives its flora from the oral surfaces contains 10^7–10^8 bacteria per ml. Most bacteria in the mouth are commensals and may have a protective role against pathogenic bacteria. Oral infections are categorized as primary, where bacteria cause diseases such as caries, chronic gingivitis, and inflammatory periodontal disease, and secondary, which aggravate existing damage associated with contaminated tissue. Antibacterial agents are used in the treatment of chronic gingivitis and effective agents, such as chlorhexidine, can persist for many hours. Antimicrobial plaque inhibitors are effective in preventing the formation of, rather than destroying, established plaque.

Antifungals

The predominant oral fungal pathogen belongs to the genus Candida, but in patients with HIV infection, less common species such as Crytococci, Histoplasma and Mucorales are often found[67]. Nystatin has been incorporated into a controlled delivery system for buccal use, but amphotericin B and clotrimazole are only available as a suspension or lozenge[68]. Two prolonged-release dosage forms have been devised for the treatment of oral candidiasis:

chlorhexidine and clotrimazole, for therapy against Candida albicans, and also benzocaine and hydrocortisone to combat the pain and inflammation secondary to a candidal infection[69]. Interestingly only chlorhexidine and clotrimazole could be delivered in a controlled manner from the mucoadhesive patches, but release of all four drugs was controlled from the mucoadhesive tablets. Optimum release of the drugs over 24 h was achieved using sodium carboxymethylcellulose and polyethylene oxide combination tablets. Recently interferon-a has also been investigated for use against fungal infections of the oral cavity[70].

Others

Commercial products which deliver drugs either buccally or sublingually are available for lorazepam for anxiety and insomnia, nicotine for smoking cessation and ergotamine for migraine treatment. The buccal route has been tried with variable degrees of success for several other drugs, including metronidazole, metoclopramide, phenazocine, propranolol, timolol, salbutamol, fenoterol and insulin. Calcium channel blockers (nifedipine, verapamil) both produce effects similar to oral doses when administered sublingually or buccally[71 72]. The buccal route has also been explored for the delivery of peptides since the mucosa is reported to lack surface-bound peptidases, and preliminary work in dogs demonstrated significant absorption of a hydrophobic lauroyl derivative of a tripeptide[35]. Thyrotropin-releasing hormone, vasopressin analogues and insulin have been investigated as potential candidates for buccal and sublingual drug delivery. Oxytocin can be delivered by the buccal route, but this is now not often used since absorption was variable, and it was of real benefit only when the cervix was already ripe[73]. Its use was therefore largely abandoned in favour of the intravenous route. Most research groups are concentrating on using the nasal route to deliver peptides since it is more permeable than the oral cavity[74].

CONCLUSIONS

The attractiveness of the buccal route of dosing is the avoidance of first-pass metabolism of drugs. Drugs which can successfully be delivered by this route need to be highly active and able to produce a pharmacological response in small amounts. Absorption appears to be somewhat erratic due to an unpredictable salivary flow washing drug into the stomach, which is then available for absorption via the small intestine. Possibly the degree of plaque formation in the mouth and hence variability in junctional epithelium exposed also affects absorption to a degree.

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