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Intraoral Drug Delivery

A Comparative Review

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Contents

Abstract . . . 171
1. Physiology and Properties of the Oral Mucosa . . . 173
2. Drug Delivery Systems for Intraoral Drug Delivery . . . 174
   2.1 Intraoral Mucoadhesive Systems . . . 174
      2.1.1 Mucoadhesive Patches . . . 174
      2.1.2 Mucoadhesive Tablets . . . 176
      2.1.3 Mucoadhesive Liquid . . . 178
   2.2 Quick-Disintegrating/Dissolving Intraoral Drug Delivery Systems . . . 178
      2.2.1 Open Matrix-Type Wafers and Tablets . . . 178
      2.2.2 Rapid-Melting Tablet . . . 180
      2.2.3 Disintegrating Film . . . 180
      2.2.4 Effervescent Tablet . . . 181
   2.3 Solid Intraoral Drug Delivery Systems . . . 181
   2.4 Aerosol Intraoral Drug Delivery System . . . 181
3. Penetration Enhancers . . . 182
4. Conclusions . . . 183

Abstract

The oral availability of many drugs is poor because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Traditionally, these drugs have been administered as parenteral drug delivery systems, which invariably leads to poor patient compliance. This has made the pharmaceutical industry look for alternative routes of drug delivery.

One possible route is via the oral cavity. This review compares the many different and novel drug delivery systems that have been developed for absorption through the oral cavity as well as those that undergo quick disintegration or dissolution in the oral cavity. Systems for oral delivery include mucoadhesive patches, films and tablets, as well as quick-disintegrating wafers, tablets and films. There are many examples of drugs that have been formulated into intraoral absorptive drug delivery systems as well as quick-disintegrating drug delivery systems.

The fact that most of the research being conducted on intraoral drug delivery systems is driven by pharmaceutical manufacturers demonstrates the need for such drug delivery systems. As we begin to discover more about oral mucosal drug delivery, and develop much more sophisticated drug delivery systems, many more drugs will be formulated as intraoral systems. There is no doubt that the need for these systems is real, and many classes of drugs could benefit from this noninvasive type of drug delivery. The challenge now is to synthesize

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drug moieties that exhibit increased absorption across the oral mucosa and are more potent in their action. Intraoral drug delivery systems are possibly one of the very few drug delivery systems that seem to be ahead of the development of new drug compounds that are effectively absorbed across tissue membranes.

To achieve optimal drug therapy, one must ensure that patients receive the correct medication, at the right dosage, and at the most convenient dosing interval. Not only the pharmacodynamic and pharmacokinetic properties of the drug, but also patient compliance factors, must be considered during optimization. Lack of patient compliance is probably the most important factor that results in suboptimal therapeutic outcome for patients.[1,2] One of the major factors determining effective patient compliance is the use of a noninvasive drug delivery system. There is no doubt that oral delivery systems are by far the most popular of all drug delivery systems.

Together with the convenience of oral administration comes an extremely harsh environment for drugs to enter. The pH of the gastrointestinal (GI) tract, as well as the presence of many enzymatic processes, precludes the formulation of many drugs as oral drug delivery systems. Most peptide and protein drugs are not administered orally because of this harsh environment.[3] Examples of other drugs that are degraded in the GI tract include ester drugs, aldehydes, ketones and alcohols.[4] This environmental factor, with the phenomenon of first-pass metabolism, has resulted in the formulation of drug delivery systems that contain high concentrations of drugs because of the low availability of the drug in the GI tract. Classes of drugs susceptible to first-pass metabolism include many β-blockers,[5] analgesics,[6] antidepressants,[7] antiretrovirals[8] and antiarrhythmics.[9] To be able to deliver metabolically unstable drugs, alternative drug delivery routes must be used and novel drug delivery systems need to be developed. Traditionally, parenteral routes have been used to circumvent these problems.

To avoid long-term parenteral therapy, current research is focused mainly on the transmucosal and transdermal routes of drug delivery. Transmucosal routes available include the nasal passage, oral mucosa, vaginal passage or rectal mucosa as sites for possible drug application. For peptide drugs requiring very low doses, the nasal route shows potential because of its somewhat large tissue permeability and its rich supply of blood. However, the nasal route has some serious disadvantages, foremost being the deleterious effect of drugs and/or adjuvants on the mucociliary cells of the nasal passage.[10] The mucociliary cells are vital for the transport of mucus and hence cleaning of the nasal cavity, as well as purification of the air that is inhaled.[10]

Like the nasal route, the rectal and vaginal routes can provide reasonably good sites for drug delivery, but low patient compliance with these routes is a problem.[11] In addition, the vaginal route is gender specific. The oral cavity, however, does not have the same problems as the other mucosal routes of drug delivery. Patient compliance is not a problem and there is no adverse physiological effect, such as mucociliary damage, that could possibly prohibit its use as a site for drug delivery. In addition, the oral mucosa is less vulnerable to damage or irritation than the nasal mucosa. Another major advantage of the oral mucosa as a site for drug delivery is that it facilitates removal in cases of emergency.

As with peroral drug delivery strategies, drugs intended to be absorbed through the oral mucosa are formulated either for an extended release period or for immediate release. Intraoral drug delivery systems have therefore been developed to achieve either of these strategies. Those intended for an extended release period are mostly the buccal adhesive drug delivery systems, which remain in the buccal cavity for as long a period as possible. The main focus of these drug delivery systems is prevention of the salivatory process in the oral cavity from washing the drug away into the rest of the GI tract.

Delivery systems that have been developed to release drug immediately in the oral cavity are primarily the fast-disintegrating and fluid drug delivery systems. In these cases, the objective can be either for quick dissolution and absorption through the oral mucosa, mainly to avoid presystemic metabolism of the drug, or for complete disintegration before swallowing, for quick therapeutic action. The quick-disintegrating forms for swallowing are perhaps the fastest growing type of delivery system in this group.

Over the years, a number of reviews have been published covering the mucoadhesive-type drug delivery systems.[11-15] This review also briefly covers mucoadhesive delivery systems, but concentrates on drug delivery systems that disintegrate rapidly in the oral cavity and are intended either for oral mucosal absorption or for a quick pharmacological effect. The technologies of the drug delivery systems are similar in both cases. To understand the rationale in developing these systems, the physiology and permea-

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bility of the oral mucosa are first discussed. The review then characterizes and compares the many varied types of drug delivery systems that have been developed for intraoral release. The major emphasis, as already stated, is on the quick-disintegration and/or quick-dissolution drug delivery systems.

1. Physiology and Properties of the Oral Mucosa

Over the years, a few researchers have characterized the oral mucosa as a route for the delivery of drugs. Reviews of absorption of drugs through the oral mucosa, from both a qualitative and a quantitative perspective, have been published;[11,16,17] these include extensive reviews of the properties of the oral mucosa and the physicochemical properties of drugs that are suitable for oral mucosal absorption. The reader is referred to these excellent reviews for more in-depth information.

The mouth of humans can be divided into four distinct regions of varying permeability characteristics that play a major role in the absorption of drugs across the oral mucosa. The four principal regions for drug delivery are the buccal cavity, the lingual area, the palate and the gingival area. Figure 1 depicts the mouth and these various regions for drug absorption. It is essentially the structure of the upper epithelial layer that distinguishes the absorption characteristics of these areas.

The oral mucosa is composed of three broad layers (figure 2). The outermost and first layer is the stratified squamous epithelium, below which is the basement membrane. The epithelial layer can actively produce cells from its basal cell layer. These longitudinal basal cells then move up through a number of intermediate layers, eventually becoming more flattened, and then shed from the surface of the epithelium. This membrane overlies the lamina propria and the submucosa. The thickness of the epithelium of the buccal mucosa is approximately three times that of the sublingual epithelium.

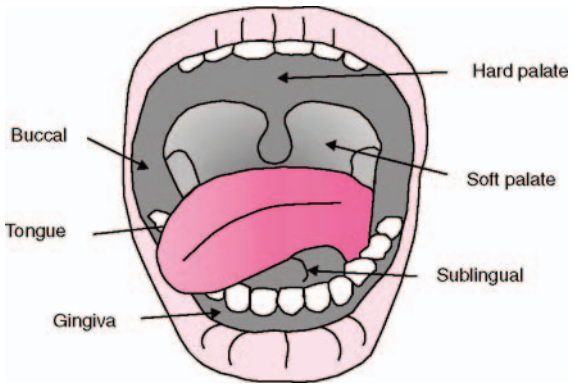

Fig. 1. Mucosal regions of the mouth.

The constitution of the epithelium also shows some variation within the different sites of the oral cavity.[18-20] The gingiva and hard palate are keratinized in a similar way to the skin epidermis; this is because they are the areas exposed to mechanical stress during eating. On the other hand, the mucosae of the soft palate and sublingual and buccal regions are not keratinized. The presence of neutral lipids, mainly ceramides and acylceramides, is thought to be responsible for the barrier function of the keratinized epithelium. In contrast, the sublingual and buccal regions have only minute amounts of ceramide and are therefore considerably more permeable.

Generally, permeability of the oral mucosa is somewhere between that of the skin and the gastric mucosa. Galey et al.[21] estimate that the permeability of the sublingual mucosa is approximately 4000 times more than that of the skin, while the hard palate is only four times more permeable. This difference is supposedly due to the presence of 'membrane coating granules' (MCGs) that are formed when cells go through differentiation from basal cells to flattened keratinous cells. When cells undergo differentiation, MCGs start forming, and at the apical cell surfaces they merge with the plasma membrane and their contents are discharged into the intercellular spaces. This occurs chiefly in the upper one-third of the epithelium. MCGs are present in both keratinized and nonkeratinized epithelia, although their composition is different in keratinized and nonkeratinized epithelia.[19] The MCGs of keratinized epithelium consist of lamellar lipid stacks and include ceramides, glucosylceramides, sphingomyelin and various other essentially nonpolar lipids. The nonkeratinized epithelium, however, contains MCGs that are nonlamellar and include cholesterol, cholesterol esters and glycosphingolipids.

Surrounding the oral epithelial cells is a thin layer of mucus, which plays a major role in cell-to-cell adhesion and oral lubrication, as well as mucoadhesion of mucoadhesive drug delivery systems.[22] A major feature of the environment of the oral cavity that plays a vital role in quick-disintegrating drug delivery systems is the presence of saliva, produced by the salivary glands. Saliva protects the soft tissues from abrasion during mastication of food. It is a predominantly aqueous fluid with variable viscosity, which depends on the time of day, the type of stimulus, and the degree of stimulation.[23] The volume of saliva produced daily ranges between 0.5 and 2L, and it is this amount of fluid that is available to

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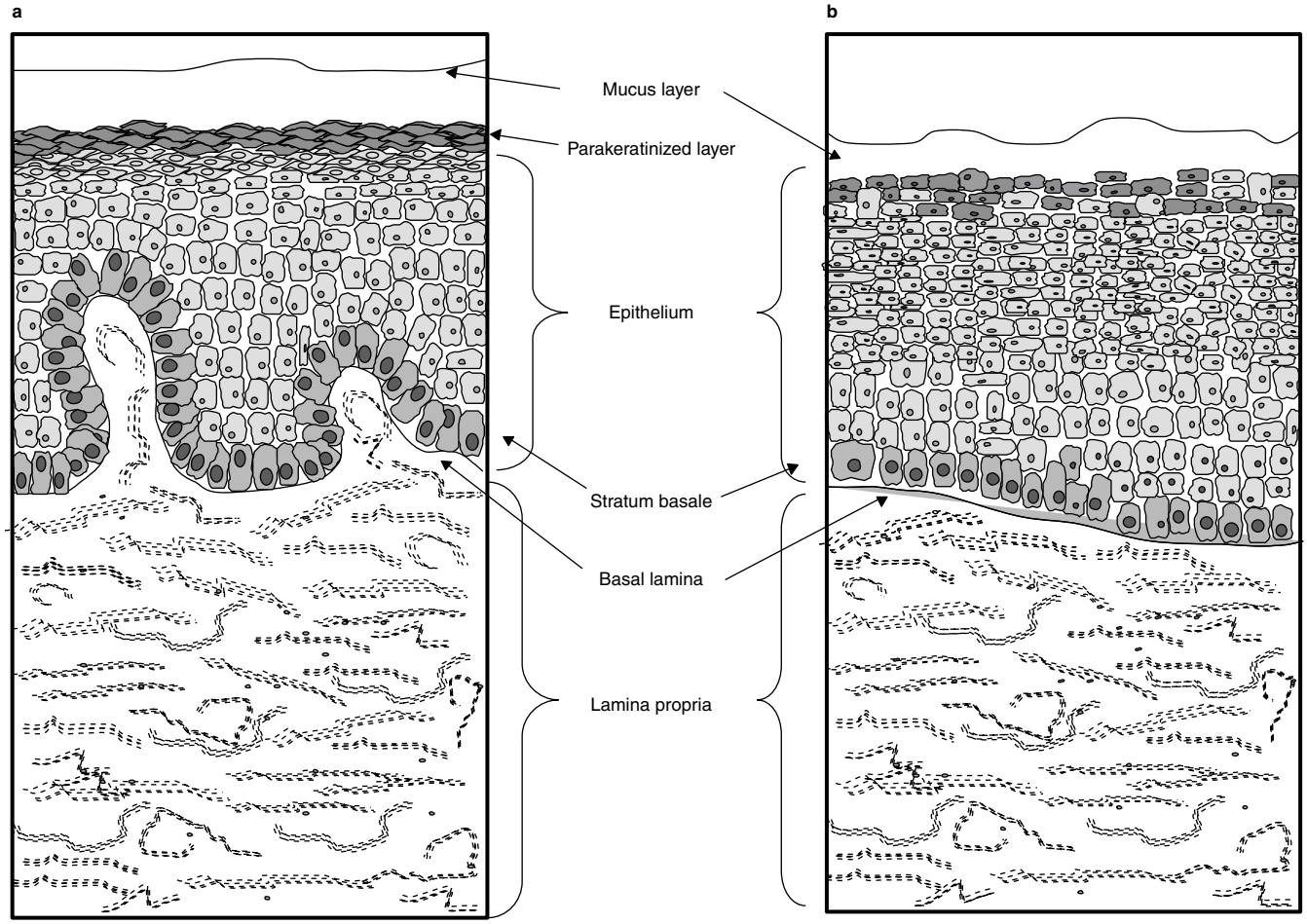

Fig. 2. Composition of the layers of (**a**) keratinized (gingiva and hard palate) and (**b**) nonkeratinized (soft palate, sublingual, and buccal regions) mucosal epithelium.

help disintegrate quick-disintegrating oral mucosal drug delivery systems.

2. Drug Delivery Systems for Intraoral Drug Delivery

Intraoral drug delivery systems designed to transfer drugs through the oral mucosa can be broadly categorized into four types: mucoadhesive buccal patches and tablets; quick-dissolving/disintegrating solid dosage forms; solid intraoral delivery systems; and aerosol intraoral drug delivery systems.

2.1 Intraoral Mucoadhesive Systems

2.1.1 Mucoadhesive Patches

Much research has been conducted on the development of intraoral mucoadhesive patches and tablets. Their advantage lies in the fact that they provide a longer period over which to deliver the drug to and through the buccal mucosa. Unlike the quick-dissolving and fluid drug delivery systems, they are not adversely affected by the risk of swallowing a large portion of the dose with saliva. Another advantage of intraoral mucoadhesive patches and tablets is their ability to provide controlled release of the amount of drug to be delivered through the oral mucosa in the same way that transdermal therapeutic systems do. Although much research has been conducted on mucoadhesive polymers, not many mucoadhesive drug delivery systems have reached commercial production. Effective bioadhesion and patient compliance still seem to be a problem.[11]

The majority of intraoral mucoadhesive patches and tablets are formulated as either solvent-cast mucoadhesive polymer discs or directly compressible flat-faced tablets of 1–3mm thickness.

Cassidy et al.[24] developed a mucoadhesive buccal patch of diclofenac sodium, an NSAID, from a prototype hydrogel. The hydrogel was formulated with 80% w/w hydroxyethyl methacrylate and 20% w/w hydrophobic difunctional macromolecular

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cross-linker. The cast hydrogel film was then placed on a piece of nonpermeable Surlyn®[1] and glued to the buccal mucosa with dental adhesive. The release of diclofenac sodium from the patches in humans was studied in a randomized, crossover design of buccal delivery and intravenous infusion. After a 30-minute delay, plasma levels of diclofenac increased to near steady-state levels of 100 μg/L by 3 hours. With each individual serving as his own control, the intravenous infusion data facilitated the calculation of a mean steady-state flux of diclofenac sodium of 2.1 ± 0.6 mg/cm^2/h across human buccal mucosa and a time lag of 1.0 ± 0.5 hours.

Shojaei et al.[25] designed a buccal mucoadhesive system for systemic delivery of acyclovir using a novel mucoadhesive consisting of copolymers of acrylic acid and poly(ethylene glycol). The buccal delivery system was prepared using an adhesive, a copolymer of acrylic acid and poly(ethylene glycol) monomethylether monomethacrylate, and an impermeable membrane to prevent excessive washout by saliva and to attain unidirectional release. Acyclovir was loaded into the copolymer film prior to lamination by a backing material. Buccal permeation of acyclovir was investigated using porcine buccal mucosa with side-by-side flow through diffusion cells at 37ºC. Buccal permeation of acyclovir from the mucoadhesive delivery system was controlled for up to 20 hours with a time lag of 10.4 hours and a steady-state flux of 144.2 μg/cm^2/h. With the incorporation of sodium glycocholate into the system, the lag time was shortened to 5.6 hours with an enhanced steady-state flux of 758.7 μg/cm^2/h. Sustained delivery of acyclovir across buccal mucosa using this mucoadhesive system was maintained for up to 22 hours.

Wong et al.[26] fabricated controlled-release buccal patches containing metoprolol tartrate in various ratios with Eudragit® NE40D. The patches were cast and cut into 2.4cm diameter discs. No backing membrane was present. Various bioadhesive polymers, namely hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose and carboxypolymer of different grades, were incorporated into the patches, to modify their bioadhesive properties as well as the rate of drug release. The incorporation of hydrophilic polymers was found to affect drug release as well as enhance bioadhesiveness. Although the high viscosity polymers enhanced the bioadhesiveness of the patches, they also tended to cause nonhomogeneous distribution of the polymers and drug, resulting in nonpredictable drug-release rates. Of the various bioadhesive polymers studied, Cekol® 700 (sodium carboxymethyl cellulose) appeared to be most satisfactory in terms of modifying drug release and enhancement of bioadhesive properties.

To obtain controlled absorption of cyanocobalamin in the GI tract, Tiwari et al.[27] investigated the use of a bilayer buccal bioadhesive patch. The patch contained a mixture of 70mg of Polyox™ 303 and cyanocabalamin (97 : 3) in the mucoadhesive layer, and 30mg of a mixture of sorbitol and magnesium stearate (99.5 : 0.5) in the backing layer. The terminal half-life of the drug after intravenous administration in four dogs was found to be 16.4 ± 2.4 hours. After administration of an immediate-release oral capsule of cyanocobalamin, the peak plasma concentration, time to peak concentration and bioavailability were 2333 ± 1469 ng/L, 2.5 ± 1.0 hours and 14.1 ± 7.9%, respectively. After administration of the buccal bioadhesive device, the corresponding values were 4154 ± 1096 ng/L, 11 ± 1.2 hours and 35.8 ± 4.1%. Significantly higher bioavailability of the drug was observed with the buccal bioadhesive device than with the immediate-release oral capsule. Therefore, the bioadhesive device appears to improve the oral bioavailability of cyanocobalamin by providing controlled delivery of the drug to the GI tract.

Senel et al.[28] designed a formulation containing chitosan for local delivery of chlorhexidine gluconate to the oral cavity. Gels (at 1% or 2% concentration) or film forms of chitosan were prepared containing 0.1% or 0.2% chlorhexidine gluconate, and their *in vitro* release properties were studied. The antifungal activity of chitosan itself and the various formulations containing chlorhexidine gluconate were also examined. Release of chlorhexidine gluconate from gels was maintained for 3 hours. Prolonged release was observed with film formulations. No lag-time was observed in release of chlorhexidine gluconate from either gels or films. The highest antifungal activity was obtained with 2% chitosan gel containing 0.1% chlorhexidine gluconate.

3M Laboratories have developed a mucoadhesive buccal patch (Cydot™) that has been tested with melatonin[29] as well as buprenorphine.[30] The Cydot™ transmucosal drug delivery system is a 0.5cm^2 flexible mucoadhesive patch containing drug in a matrix mixture of polyisobutylene and polyacrylic acid. The patch is applied to the groove above and between the canine and premolar teeth of the superior maxillary gum.

In June 2002 Atrix Laboratories announced the development of their Bio-Erodible Muco-Adhesive disc (BEMA™).[31] It is a

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unique polymer-based system that delivers systemic levels of drugs quickly across oral mucosal tissues. The BEMA™ film is a small, semisoft disc that adheres to the mucosa, such as the side of the mouth, and delivers the drug as the film bioerodes. There is no need to remove the film, because it dissolves with the moisture from the mucosa. The company claims that the versatile BEMA™ system can incorporate a wide variety of drugs, including proteins and peptides, which can be loaded into the mucoadhesive layer for delivery into the mucosal tissue while minimizing drug release into surrounding tissues or cavities.

2.1.2 Mucoadhesive Tablets

Mucoadhesive intraoral tablets have the advantage that the technology used to produce them is usually the same process and compression technology used to produce conventional tablets. This therefore makes them a very attractive dosage form from a manufacturing point of view. They do, however, have the limitation that a large portion of the active drug is swallowed by the patient, which precludes drugs that are slowly absorbed through the oral mucosa and are also extensively metabolized or not stable in the GI tract.

Anlar et al.[32] prepared buccoadhesive controlled-release tablets for the delivery of morphine sulfate by compression of hydroxypropyl methylcellulose (HPMC) with carbomer, which served as the bioactive adhesive compound. The release behavior of systems containing 30mg of morphine sulfate and various amounts of the two polymers was found to be non-Fickian. The adhesion force was significantly affected by the mixing ratio of HPMC and carbomer in the tablet, and the weakest adhesion force was observed at a ratio of 1 : 1 (HPMC : carbomer). Interpolymer complex formation was confirmed between HPMC and carbomer in acidic medium by turbidity, viscosity and Fourier Transform InfraRed (FT-IR) measurements. The amount absorbed (percentage of the drug loaded) of the controlled-release buccoadhesive tablets in six healthy volunteers was 30% ± 5%.

To provide quicker relief of gastric acid problems as well as a convenient dosage form that does not require water, Yong et al.[33] developed an effective omeprazole buccal adhesive tablet with excellent bioadhesive force and good drug stability in human saliva. The omeprazole buccal adhesive tablets were prepared with various bioadhesive polymers, alkali materials and croscarmellose sodium. The physicochemical properties of the tablets, such as bioadhesive force and drug stability in human saliva, were investigated. The release and bioavailability of omeprazole delivered by the buccal adhesive tablets were studied.[33] As bioadhesive additives for the omeprazole tablet, a mixture of sodium alginate and hydroxy propyl methylcellulose (HPMC) was selected. The omeprazole tablets prepared with bioadhesive polymers alone had bioadhesive forces suitable for a buccal adhesive tablet, but the stability of omeprazole in human saliva was not satisfactory. Among the alkali materials, only magnesium oxide could be an alkali stabilizer for omeprazole buccal adhesive tablets because of its strong waterproofing effect. Croscarmellose sodium enhanced the release of omeprazole from the tablets; however, it decreased the bioadhesive forces and stability of omeprazole tablets in human saliva. The tablet composed of omeprazole/sodium alginate/HPMC/magnesium oxide/croscarmellose sodium (20/24/6/50/10mg) could be attached on the human cheek without disintegration, and it enhanced the stability of omeprazole in human saliva for at least 4 hours and gave fast release of omeprazole. The plasma concentration of omeprazole in hamsters increased to a maximum of 370 μg/L at 45 minutes after buccal administration and continuously maintained a high level of 146–366 μg/L until 6 hours. The buccal bioavailability of omeprazole in hamsters was 13.7% ± 3.2%. These results demonstrate that the omeprazole buccal adhesive tablet would be useful for delivery of formulation of omeprazole that degrades very rapidly in acidic aqueous medium and undergoes hepatic first-pass metabolism after oral administration.

Many studies have shown that topical buccal therapy with corticosteroids is useful in controlling ulcerative and inflammatory mucosal diseases. This local treatment is based on the concept that high activity of corticosteroids can be produced at the site of administration and, at the same time, the occurrence of systemic adverse effects can be minimized or avoided. Ceschel et al.[34] developed a mucoadhesive tablet formulation for buccal administration of hydrocortisone acetate. They developed three types of tablet containing three different mucoadhesive components, namely, HPMC, carboxyvinyl polymer and polycarbophyl, at three different concentrations of 10%, 20% and 30%, resulting in nine different formulations. Mucoadhesion, *ex vivo* permeability and *in vivo* behavior results notably differed among tablets, depending on the quality and quantity of the mucoadhesive component. Permeability tests showed that all the tablets provided satisfactory drug permeability flux, compared with the flux from a saturated solution of hydrocortisone acetate in water. An overall comparison of results showed the tablets containing 20% carboxvinyl polymer were the best formulation among those developed, as it rapidly

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adhered to the mucosa. They also remained at the application site for the longest period (2 hours 37 minutes), with the exception of carboxvinyl polymer at the 30% level, which adhered for 3 hours 15 minutes, but did not show a good adhesion effect, as it required more than one attempt to get the tablet to adhere to the gingiva.

Treatment of oropharyngeal Candida infections requires an effective therapeutic treatment and appropriate dosage form. Kuipers et al.[35] used lactoferrin as a potential drug candidate for a mucoadhesive tablet for buccal application. The tablets they produced could be manufactured on high-speed tabletting machines, but they could be manufactured only when the protein contained at least 7% moisture. The tablet contained sodium alginate both for its release-controlling properties and for its mucoadhesive properties. Furthermore, phosphate buffer was added to keep the pH of the saliva in the mouth within the range of 6.5–7.5. In this pH range, lactoferrin has been shown to have its highest activity against Candida growth. The tablet formulation containing lactoferrin had the same antifungal properties as lactoferrin alone, because in most cases identical inhibitory concentrations were observed against several clinical isolates of *Candida albicans* and *C. glabrata*. In human volunteers the tablets, containing 250mg lactoferrin and placed in cheek pouch, were able to keep the lactoferrin concentration in the saliva at effective levels for at least 2 hours, while the pH of the saliva remained within the desired range.

Giunchedi et al.[36] investigated the development of buccal tablets based on chitosan microspheres containing chlorhexidine diacetate. The microparticles were prepared by a spray-drying technique; their morphological characteristics were studied by scanning electron microscopy and the in vitro release behavior was investigated in pH 7.0 United States Pharmacopoeia (USP) buffer. Chlorhexidine in the chitosan microspheres dissolves more quickly *in vitro* than does chlorhexidine powder. The antimicrobial activity of the microparticles was investigated as minimum inhibitory concentration, minimum bacterial concentration and killing time. The loading of chlorhexidine into chitosan is able to maintain or improve the antimicrobial activity of the drug. The improvement is particularly high against *C. albicans*. This is important for a formulation whose potential use is against buccal infections. Drug-empty microparticles have antimicrobial activity due to the polymer itself. Buccal tablets were prepared by direct compression of the microparticles with mannitol alone or with sodium alginate. After their *in vivo* administration, the determination of chlorhexidine in saliva showed the capacity of these formulations to give prolonged release of the drug in the buccal cavity.

In another attempt to produce an intraoral mucoadhesive drug delivery system, Medlicott et al.[37] investigated the formulation of a tooth-bonded drug delivery film. Films containing 20% chlorhexidine base (particle size 63–125μm) in poly(epsilon-caprolactone), MW 35 000–45 000, were prepared by solvent evaporation and sections attached to the mesiolingual and mesiobuccal surfaces of the lower first molar in healthy volunteers. Saliva (<1.5μL) was collected on Periopaper®, and chlorhexidine concentrations measured by high performance liquid chromatography were typically higher in the area immediately adjacent to the tooth-bonded film sections and lower at more distant sites. Analysis of variance of chlorhexidine concentrations, adjacent to the film sections, showed concentrations were significantly different on the buccal and lingual sides of the tooth and depended on the time of sampling ($n = 5$; $p < 0.05$).

To produce a medicated dressing that patients can use and apply, Ruben[38] developed a flexible intraoral bandage that remains securely in place in a patient's mouth without irritating the surrounding tissue. The bandage comes in the form of a kit, which includes a hydrolyzable powder/water-wettable fiber mixture enclosed in a flexible, water-permeable, nonstick envelope. The envelope is immersed in water or medication so that the liquid is absorbed through the envelope to wet the hydrolyzable powder/water-wettable fiber mixture to form a moldable tacky gel. The envelope is then removed from the gel and the gel is manually molded and placed in a desired location in a patient's oral cavity. The kit can also be used as a drug delivery system to deliver medication to a patient through the oral cavity.

In further developments of intraoral delivery, Yukimatsu et al.[39] have formulated a tablet that is designed for both immediate and controlled release. The device is a tablet-shaped mucoadhesive system composed of two layers. Figure 3 illustrates this bilayer mucoadhesive tablet system. The upper layer is a fast-release layer and the lower layer is a mucoadhesive sustained-release layer. It is designed to be applied between the buccal and gingival mucosa. Isosorbide dinitrate and nifedipine were used as model drugs. The fast-release layer was composed of 20% drug dispersed in a solid matrix of D-mannitol and polyvinylpyrrolidone. The sustained-release layer was composed of 80% drug in a polymer matrix of polyvinylpyrrolidone of high molecular weight and polyacrylic acid. This transmucosal therapeutic system (TmTs) achieved rapid and sufficient adhesion to the gingival

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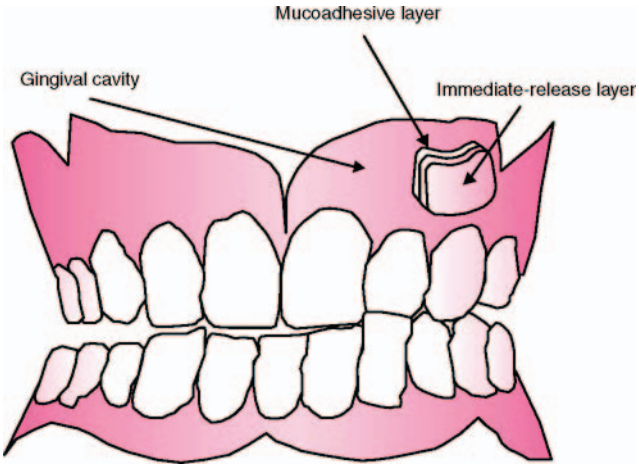

Fig. 3. Transmucosal therapeutic system, a bilayer mucoadhesive system, showing fast-release upper layer and the mucoadhesive sustained-release layer.

mucosa and also achieved effective and prolonged plasma drug concentrations.

2.1.3 Mucoadhesive Liquid

In the field of oral hygiene, many products are available. The most popular are the liquid oral rinse formulations, which are pleasantly flavored and easy to use. However, the short contact time with the oral mucosa is not desirable as a drug delivery system. Most oral infections or diseases benefit from more prolonged contact with the mucosa, even those used as breath fresheners. To address this problem, Access Pharmaceuticals has developed their MucoAdhesive Liquid technology, which provides an extended coating of the oral mucosa and can present pharmaceutically active ingredients to the entire oral cavity over an extended period.[40] This extension of contact time is due to the pseudoplastic nature of the liquid and its mucoadhesiveness. Patients exposed to long treatments of chemotherapy and radiation often develop oral mucositis, a painful ulcerative condition that is an adverse effect of the treatment. Unlike minor aphthous ulcers, which usually occur one at a time (more than two or three ulcers at a time is rare), mucositis can present as multiple ulcers appearing anywhere in the mouth. Access Pharmaceuticals has developed a mucoadhesive liquid formulation of amlexanox to coat the entire oral cavity by simply swirling the liquid in the mouth. A phase II clinical study was conducted to evaluate the potential of amlexanox for prevention and treatment of mucositis. The Oral Mucositis Assessment Scale (OMAS) was used to quantify the degree of mucositis and assessment of pain. Results indicated that the mucoadhesive liquid formulation of amlexanox compared favorably with standard treatments used for mucositis.[40] With the aid of a preclinical model, Access Pharmaceuticals is currently optimizing the formulation of the MucoAdhesive Liquid technology for the indication of prevention and treatment of mucositis and plans soon to begin a clinical study of the optimized formulation.

2.2 Quick-Disintegrating/Dissolving Intraoral Drug Delivery Systems

Quick-disintegrating/dissolving tablet drug delivery is now a well accepted and important new class of drug delivery system. Intraoral delivery of drugs is not a new phenomenon. Sublingual nitroglycerin, verapamil HCl, and isoproterenol (isoprenaline) tablets, to name a few, have been on the market for many years. However, only since Wyeth Pharmaceuticals (Collegeville [PA], USA) in the late 1970s developed the Zydis® fast-dissolving wafer has the market grown quite dramatically.[41] Today the drug delivery systems are known as fast-dissolve, quick-dissolve, rapid melt, quick-disintegrating, etc., all representing the same type of drug delivery system, which is referred to in this review as the quick-disintegrating intraoral drug delivery system. The term disintegrating is a little more accurate than dissolving. Systems that disintegrate in the oral cavity, but are primarily intended for swallowing, are also discussed here, as the type of drug delivery system is essentially the same for drugs that are intended to be swallowed or absorbed intraorally.

Quick-disintegrating intraoral drug delivery can be accomplished by a number of different technologies, including direct compression, wet granulation and freeze-drying. They also exhibit different methods of disintegration to release the drug to the oral mucosa. Whatever mechanism is used, the drug delivery systems all disintegrate in the patient's mouth within a minute without the need of water or chewing. This is clearly why there is such good patient compliance with these systems, and also why they are receiving so much interest from manufacturers.

2.2.1 Open Matrix-Type Wafers and Tablets

Zydis® was the first quick-disintegrating intraoral drug delivery system to be commercialized on a large scale. It is a freeze-dried wafer, made from various standard tablet adjuvants.[41,42] Figure 4 illustrates the production of the Zydis® system. The wafer is based on the concept of forming an open matrix network containing the active ingredient. This technology pioneered the concept of quick-disintegrating drug delivery systems. The open matrix is a network of water-soluble or water-

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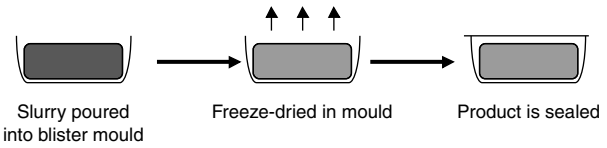

Fig. 4. Production of Zydis® freeze-dried wafer.

dispersible carrier materials, generally of low density and containing interstices or pores dispersed throughout. When Zydis® units are put into the mouth, the freeze-dried structure disintegrates within 2–3 seconds, releasing the drug. The drug then disperses or dissolves in the patient's saliva, is swallowed, and is absorbed in the normal way from the GI tract. The quick disintegration is also suitable for drugs that are intended for rapid absorption in the oral cavity. In these cases the bioavailability of Zydis® wafers increases the bioavailability of the drug.

The Zydis® open matrix contains a number of different adjuvants all included for specific outcomes. The bulk of the wafer contains solutions of polymers such as gelatin and dextran to form the amorphous glassy structure for strength. Saccharides such as mannitol or sorbitol are added to give it crystallinity. Other additives include preservatives, suspending agents, buffers, colorants and flavors, permeation enhancers, and glycine to prevent collapse and shrinkage during the freeze-drying process. The slurry formed is then dosed accurately into preformed blister packs, frozen, and then freeze-dried. Once dried, the units in the blister packs are sealed with peelable backing foil.

A major advantage of the Zydis® system is that nonaqueous solutions of active drugs can be dosed into placebo wafers. The organic solvent can then be evaporated and the recrystallized drug is deposited in the pores of the matrix. So far drugs such as oxazepam,[43] piroxicam,[44,45] rizatriptan,[46] zolmitiptan,[47] olanzepine,[48] selegiline HCl,[49] ondansetron,[50] and loratadine,[51] to name a few, have already been produced using the Zydis® technology.

To produce a tablet that is not very fragile, and does not require freeze-drying, Pebley et al.[52] developed a tablet that includes a partially collapsed matrix network that has been vacuum-dried above the collapse temperature of the matrix. The matrix is partially dried below its equilibrium freezing point. Vacuum-drying the tablet above its collapse temperature instead of freeze-drying it below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva. This results in a tablet that is partially collapsed on the surface, which gives the tablet enhanced structural integrity, such that it can be removed from a blister pack in the normal way (figure 5). The matrix network of the tablet typically includes a gum, a carbohydrate and the drug.

Tatara et al.[53] have described a method and an apparatus in their patent that is capable of manufacturing a tablet that undergoes quick disintegration in the oral cavity. It has sufficient porosity to enable disintegration in the oral cavity in a very short time, typically 3–5 seconds. The method for manufacturing the tablet comprises steps of punching a tablet out of a pharmaceutical composition containing one or more medicinal agents and one or more water-soluble saccharides under pressure between 0.20 and 0.01 tonnes/cm^2. The tablet is then shaped by moisturizing and drying it, while transferring it without causing it to drop from the conveyor belt. The resultant tablet has a porosity between 20% and 40%. Figure 6 illustrates the production process. Unlike the Zydis® technology, the production process is a continuous one.

Yamanouchi Pharmaceutical Co. Ltd has conducted extensive studies on an intrabuccally dissolving compressed tablet that can be produced under standard manufacturing conditions.[54] The tablet is referred to as the WOWTab® (With-Out-Water tablet). Until 1999, at least nine different formulations had been produced using the WOWTab® technology. Yamanouchi Pharmaceutical Co. found that when a raw material obtained by granulating a low moldability saccharide showing quick disintegration and dissolution was combined with a high moldability saccharide, and subjected to compression, the resulting tablet exhibited quick disintegration and dissolution in the buccal cavity (figure 7). The tablets have adequate hardness to withstand the production process and distribution stages. Quick disintegration is accomplished by mixing a low-moldability saccharide with a high-moldability saccharide. The high-moldability saccharide is used as the binding agent in the granulation step instead of commonly used water-soluble polymer binders. The term 'saccharide having low moldability properties' means a saccharide that generally shows a hardness of 0–2kg when 150mg of the saccharide is made into a tablet using a

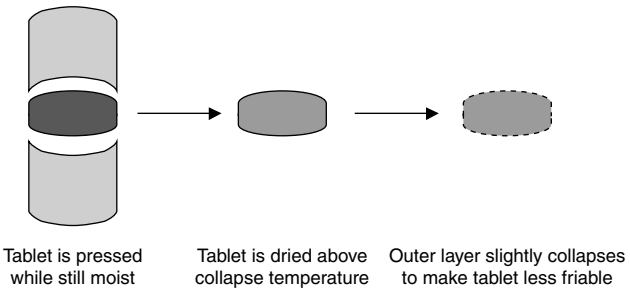

Fig. 5. Production procedure of a partially collapsed tablet.

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punch of 8mm diameter under a pressure of 10–50 kg/cm^2. Examples of such saccharides include lactose, mannitol, glucose, sucrose and xylitol, of which lactose and mannitol are preferred. These saccharides may be used alone or as a mixture of two or more. The term 'saccharide having high moldability properties' means a saccharide that generally shows a hardness of 2kg or more when 150mg of the saccharide is made into a tablet using a punch of 8mm diameter under a pressure of 10–50 kg/cm^2. Examples of such saccharides include maltose, maltitol, sorbitol and oligosaccharides, of which maltose and maltitol are preferred. These saccharides may be used alone or as a mixture of two or more. The intrabuccally dissolving tablet uses a saccharide with low moldability as its main component, with a blending ratio of a high-moldability saccharide to the low-moldability saccharide of 2–20% by weight, preferably 5–10% by weight. This gives the tablet adequate hardness during manufacture and storage, or when it is taken out of the package.

According to Cousin et al.,[55] a quick-disintegrating tablet can be formulated by adding one or more disintegrating agents of the carboxymethylcellulose type or insoluble reticulated poly(vinylpyrrolidinone) (PVP) type, together with one or more swelling agents (which may consist of a carboxymethylcellulose, a starch, a modified starch or a microcrystalline cellulose) and possibly a direct compression sugar consisting, for example, of 92% of dextrose. In their patent, they disclose that it was possible to introduce into a tablet containing the above disintegrating agents, an active substance in the form of coated or noncoated microcrystals or microgranules. This, of course, is useful for drugs that have a particularly unpleasant taste. Consequently, the rapidly disintegratable multiparticulate tablet, known as Flash Tab®, according to the patent, can disintegrate in the buccal cavity within 60 seconds.

The Flash Dose® tablet developed by Fuisz Technologies Ltd can dissolve in the mouth of the patient in less than 10 seconds.[56]

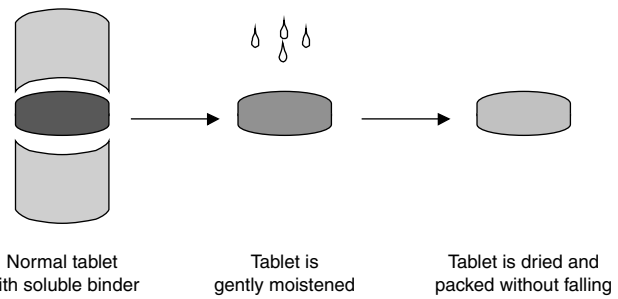

Fig. 6. Production of a moistened soluble binder quick disintegration tablet.

The most highly dissolvable units have been described as literally 'exploding' in the mouth. The Shearform™ technology used by Fuisz Technologies Ltd is a process in which a unique blend of sugars is placed in a fast-spinning machine and subjected to flash heat to produce long, cotton candy-like fibers known as 'floss'. The untreated floss can then be cured by being subjected to environmental conditions of heat, moisture and pressure that induce crystallization. For example, increasing the heat under substantially constant moisture conditions can cure the fibers. Subjecting the floss to microwave energy can increase the heat. Crystallization modifiers such as surfactants, dextrose, polyethylene glycol and polypropylene glycol can enhance curing. These modifiers generally provide controlled acceleration of crystallization while the matrix is bound. When blended with coated or uncoated microspheres containing active drug, the floss is compressed into tablets on standard tabletting equipment (figure 8). Through the use of a high-speed tablet press, Fuisz can turn out a maximum of 150 000 rapid-dissolve tablets per hour.[57]

2.2.2 Rapid-Melting Tablet

Lipid waxy binders that rapidly melt at body temperature have also been used to prepare quick-disintegrating intraoral tablets. A novel rapid-melt, semisolid, molded composition including at least one melted wax binder, a salivating agent, a diluent/bulking material, a slipping agent and an active material was recently patented by Cherukuri.[58] A unique feature of the tablet is that the composition becomes liquid upon application of pressure. The semisolid compositions rapidly melt upon application of pressure by the tongue of the patient, thus forming a liquid carrier for the active ingredients contained therein. The waxy binder that is used consists of various combinations of cocoa butter and lecithin; salivating agents include, edible emulsifiers and food acids. The final tablets may also be coated to prevent melting on storage in warmer climates.

2.2.3 Disintegrating Film

To develop a drug delivery system that is both mucoadhesive and quick-disintegrating, Zerbe et al.[59] have filed a patent describing a water-soluble film for oral administration with instant wettability. The film comprises water-soluble polymers, one or more polyalcohols and one or more pharmaceutically or cosmetically active ingredients. Optionally, the formulation may contain a combination of certain plasticizers or surfactants, colorants, sweetening agents, flavors, flavor enhancers or other excipients commonly used to modify the taste of formulations intended for

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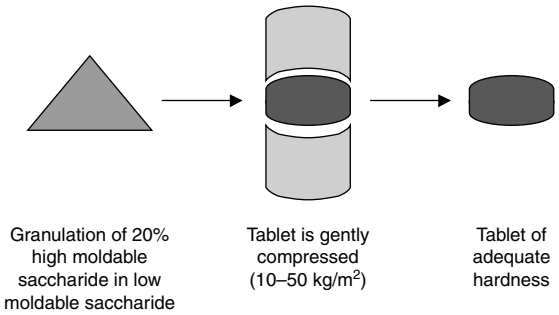

Fig. 7. Production of the WOWTab®.

application to the oral cavity. The film exhibits instant wettability and immediate softening after application to the mucosal tissue. At the same time the dry film has sufficient tensile strength for film forming, cutting, slitting and packaging operations. Drying of the film is carried out in a high-temperature air bath using a drying oven, drying tunnel, vacuum drier or any other suitable drying equipment that does not adversely affect the active ingredient(s) or flavor of the film. To reliably avoid an adverse feeling in the mouth, a dry film thickness of 70μm should not be exceeded.[59]

2.2.4 Effervescent Tablet

Like normal oral effervescent tablets that disintegrate quickly in a glass of water, a saliva-activated effervescent tablet (OraSolv®) for quick disintegration in the mouth has been produced by Cima Labs Inc.[60] The effervescent disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide a distinct sensation of effervescence when the tablet is placed in the patient's mouth. The effervescent sensation is not only pleasant to the patient but also tends to stimulate saliva production, thereby providing additional fluid to aid in further effervescent action. Thus, once the tablet is placed in the patient's mouth, it disintegrates rapidly and completely without any voluntary action by the patient. Even if the patient does not chew the tablet, disintegration proceeds rapidly. Tablets based on the OraSolv® technology require Cima's proprietary packaging system, PakSolv®. To accommodate normal packing, the company has developed DuraSolv®, which is a more robust and durable oral dosage form than OraSolv®. DuraSolv® products may be packaged in conventional packaging, such as foil pouches or bottles, at more efficient production rates and at a lower cost than OraSolv® products. Although the tablets disintegrate rapidly in the mouth, they are mainly intended to be swallowed once they have disintegrated. More recently, Cima Labs Inc. has developed OraVescent® tablets for intraoral absorption of drugs.[61] The OraVescent® tablet contains an additional pH-adjusting substance in combination with the effervescent technology for promoting intraoral absorption of drugs.

2.3 Solid Intraoral Drug Delivery Systems

Oral lozenges have been used for many years and have proved to be a very popular drug delivery system for treating local mouth diseases and sore throats.[62] Most are manufactured as candy-type lozenges or tablets without disintegrants and are intended to be sucked by patients. The drugs that have traditionally been used have very few systemic adverse effects, and there has never really been concern about the amount of drug swallowed by the patient. Lately, however, more potent drugs with much lower doses have been placed in these types of lozenges, which are mainly used for their quicker intraoral absorption properties.[63-66]

One of the first lollipop-type drug delivery systems designed for transmucosal drug delivery was developed by Mock et al.[67] in 1986. These lollipops were made by heating a candy base to 150ºC and then adding 0.1–5mg fentanyl citrate crystals when the base had cooled to 121ºC. After this, the candy and fentanyl mixture was poured into molds at 107ºC, a stick was added, and the lollipops were allowed to cool and harden before removal from the molds. Results indicated that lollipops of 0.5 and 1.0mg of fentanyl produce significant analgesia and sedation for short periods (1–2 hours) with few adverse effects and little respiratory depression. Today, this system is one of the few oral transmucosal drug delivery systems to be commercialized. It is marketed as Actiq® to treat breakthrough cancer pain.[68] Figure 9 illustrates the Actiq® drug delivery system.

2.4 Aerosol Intraoral Drug Delivery System

By tradition, aerosol sprays have been used to treat local diseases and ailments in the oral cavity. As with liquid systems, the intention was not for extensive systemic absorption, and the oral cavity was not treated as a site for systemic drug absorption.

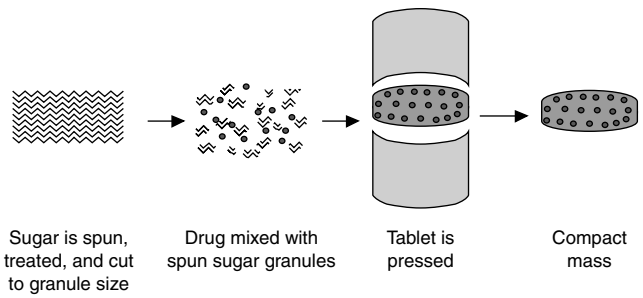

Fig. 8. Production of the Flash Dose®.

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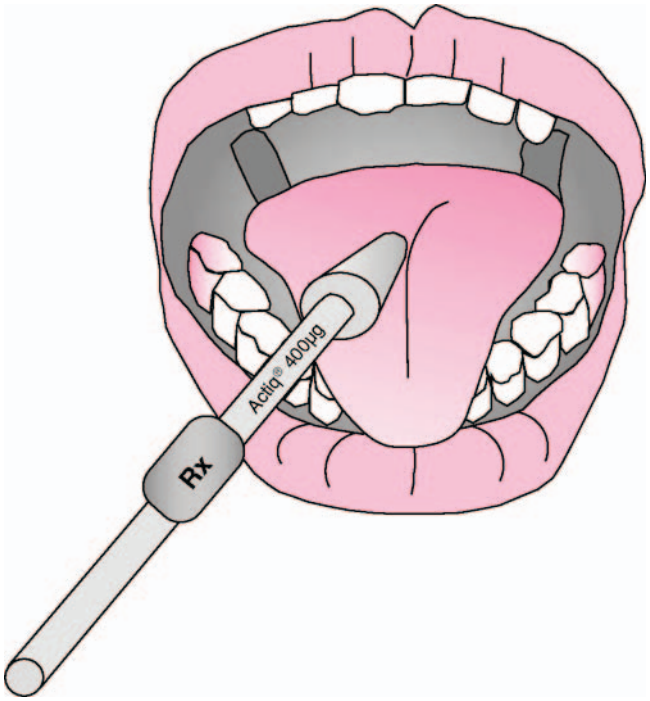

Fig. 9. Actiq® drug delivery system.

However, the failure of subcutaneous insulin to effectively, safely and painlessly control postprandial glucose levels has led to the development of many substitute insulin drug delivery systems.[69] Recently, an oral aerosol system (Oralin®), was developed.[69] This system delivers accurate insulin doses into the mouth by use of a metered-dose aerosol. Mouth deposition is dramatically increased compared with that of conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal lining and in the oropharynx regions, and it provides the plasma insulin levels necessary to control postprandial glucose rise in patients with diabetes mellitus.

Nitroglycerin has also been formulated in a lingual aerosol spray. The time required for tablet dissolution is known to vary from one person to another and this period delays the bioavailability of the medication.[70] In contrast, the lingual spray is directly absorbed, and studies based on symptom relief have suggested that the onset of action of the lingual spray could be faster than that of the sublingual tablet.[70-72]

3. Penetration Enhancers

Improved patient acceptance and compliance, as well as the accessibility of the oral mucosa, are positive factors for development of intraoral drug delivery systems. However, the generally low permeability of the oral mucosa is a major constraint to delivery of drugs via this route. The most common approach in current research to increase the permeability of the oral mucosa is incorporation of penetration enhancers into intraoral drug delivery systems.[73] A penetration enhancer should be nontoxic, pharmacologically and chemically inert, nonirritant and nonallergenic. If not, the tissue where it is placed should at least revert to its normal integrity and barrier properties upon removal of the enhancer.

Until now, most compounds used as intraoral mucosal penetration enhancers are the agents generally used to compromise the barrier function of the mucosa. In contrast to studies conducted on the skin, little work has been targeted specifically to the oral mucosa. As mentioned above, the paracellular route via passive diffusion is the most common route for drugs to permeate across the oral epithelium. Nevertheless, a few specialized transport systems are present in the oral mucosa.[74]

Absorption enhancers can be divided into five broad groups: chelators, surfactants, fatty acids, nonsurfactants and inclusion complexors.[11] To date, the most promising compounds are the bile salt surfactants and chitosan polymer derivatives. Because of their surfactant properties, and their ability to interact with lipids, bile salts have been extensively studied as possible penetration enhancers. They have also been used extensively to enhance the absorption of drugs through various other epithelia such as nasal, rectal, pulmonary, ocular and vaginal.[75-77] Bile salts are thought to increase permeability through extraction of membrane protein or lipids, membrane fluidization and reverse micellization.[78] This then results in the creation of pseudo-aqueous channels in the membrane. There are, however, some concerns about irritancy and damage to the mucosal membrane that occurs when using bile salts as penetration enhancers. To address this problem, Senel and Hincal[79] studied the effect of various bile salts on buccal permeation of a number of model drugs, as well as the mucosal irritation of the bile salts. Their results showed that bile salts were quite capable of enhancing the permeation of fluorescein isothiocyanate, morphine sulfate and morphine HCl across porcine buccal mucosa. As a significant accumulation of the bile salt sodium glycocholate in the buccal tissue was observed, studies on reversibility of the enhancing effects of bile salts on the tissue were carried out *in vivo* for assessment of the safety of bile salts as penetration enhancers.[80] Changes were observed in buccal epithelium right after 4-hour application of the bioadhesive tablet incorporated with a bile salt, whereas the control tablet did not cause any visible change or damage to the buccal mucosa. Further studies were carried out to investigate the reversibility of these

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changes.[81] Light and electron microscopy results showed that after removal of the tablet, epithelial cells recovered gradually within 24 hours, indicating that mucosal irritation is reversible. Nakane et al.[82] also conducted a comparable study using bile salts and luteinizing hormone-releasing hormone, and obtained very similar results.

More recently, chitosan has shown potential in enhancing the absorption of small polar molecules and peptide/protein drugs through nasal mucosa in animal and human studies[83-86] as well as buccal mucosa.[87,88] The promising result from these studies was that no notable damage to the mucosa was detected. Therefore, besides chitosan's improved permeability-enhancing properties, the lack of toxicity, improved biocompatibility and biodegradability make chitosan a potential enhancer for intraoral mucosal penetration.

According to Oh and Ritschel,[89] the buccal delivery of insulin to rabbits results in a bioavailability of only 3–5%. In a study of the effect of various penetration enhancers on the buccal bioavailability of insulin, they found that all the following substances increased the bioavailability of insulin: ethylenediaminetetraacetic acid (EDTA), sodium dextransulfate, sodium methoxysalicylate, sodium taurocholate and Brij™ 35 (polyoxyethylene ether). EDTA had the lowest effect and Brij™ 35 the highest, at 12% bioavailability. Aungst and co-workers[90,91] have also studied a number of nonionic surfactants, steroidal detergents and sodium lauryl sulfate, which also showed some promise in enhancing the absorption of insulin across the buccal mucosa.

Traditional topical penetration enhancers have also been tried in buccal penetration enhancement. Azone, one of the first topical penetration enhancers on the market, has been investigated.[92,93] Although the results of the studies did show an increase in the rate of penetration of drugs through buccal mucosa, the effect was slight and did not last long.

Cyclodextrans have also been investigated for enhancement of penetration of various drugs through the buccal mucosa. However, once again, enhancement was not particularly significant and was achieved only with modified cyclodextrans such as condensation products of β cyclodextran.[94]

Unfortunately, enhancement of the permeability of drugs across the buccal mucosa is directly proportional to disruption of the epithelium and the more damage that is done to the mucosa. This makes the long-term use of penetration enhancers not feasible at the moment, as the added benefit does not compensate for the increase in adverse effects through mucosal damage.

4. Conclusions

The fact that most of the research being conducted on intraoral drug delivery systems is driven by pharmaceutical manufacturers demonstrates the need for such systems. As we begin to discover more about oral mucosal drug delivery, and develop much more sophisticated drug delivery systems, many more drugs will come on line. There is no doubt that the need for these systems is real, and many classes of drugs could benefit from this noninvasive type of delivery. The challenge now is to synthesize drug moieties that exhibit increased absorption across the oral mucosa and are more potent in their action. Intraoral drug delivery systems are possibly one of the very few drug delivery systems that seem to be ahead of the development of new drug compounds that are effectively absorbed across tissue membranes. It is hoped this backlog of potent drugs will be developed as we progress in biotechnology and develop more peptide drugs for human usage. Fortunately, these drugs are much more potent than their nonpeptide companions are, and they are sufficiently absorbed across the oral mucosa.

To date, many penetration enhancers of diverse chemical nature have been tested and found to be effective in facilitating buccal drug administration *in vitro*. Nevertheless, no formulation for buccal administration containing a penetration enhancer has been commercialized so far. It is generally considered that oral mucosal damage caused by bile salts would be reversible and less serious than nasal mucosal damage due to the nature of the oral mucosa. The development of well tolerated, and non-irritating penetration enhancers will also advance this route of drug delivery. This field is, however, in its infancy, and much needs to be done. We urgently need to find a system that does not adversely affect the mucosa in the long term. Chronic toxicity studies need to be conducted on the long-term effects on mucosal tissues. Other methods of decreasing the short-term barrier activity of the membranes need to be explored and developed. The generation of novel, more potent permeation enhancers, based on an improved knowledge of the absorption membrane in combination with the appropriate delivery systems, will strongly improve the bioavailability of mucosally applied peptide drugs.

For intraoral absorption of drugs, the problem of effective taste masking without adversely affecting the dissolution of drugs needs to be solved. Coating of unpleasant-tasting drugs does affect quick absorption, which is needed after quick disintegration. If absorption does not occur quickly enough, much of the dose is lost in the saliva during swallowing. This undoubtedly leads to erratic dose-

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response relationships and variable therapeutic effects. In itself, this is a major hurdle to overcome and will preclude the formulation of many drugs into intraoral drug delivery systems. Other means of taste masking that do not adversely affect the dissolution rate will have to be found.

Even though intraoral drug delivery systems are in their infancy, and there are a few hurdles to overcome, the market demand for such systems will continue to grow. This need to effectively deliver drugs will grow exponentially as more and more peptide drugs are synthesized. The demand for an effective noninvasive drug delivery route will become even more urgent.

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