

Oral local drug delivery and new perspectives in oral drug formulation

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Modern pharmaceutical science has provided us with a wide range of substances to be administered with a wide large variety of dosage forms. Local drug delivery systems have been used for a long time; in particular, for the local therapy of diseases affecting the oral cavity. Although these diseases are often extremely responsive to local therapy, the mouth often presents various difficulties in the application of topical compounds (owing to saliva and the mouth's different functions), resulting in a short retention time of dosage forms with a consequent low therapeutic efficacy. To resolve these limitations, research today concentrates on the development of bioadhesive formulations. This review focuses on the permeability features of oral mucosa, the rationale of oral local drug delivery, and new potential bioadhesive local delivery systems. Furthermore, the most promising mucoadhesive systems proposed to locally treat oral diseases are discussed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:e25-e34)

Oral mucosa diseases are among the most common diseases affecting humans, and they can be effectively treated by topical therapeutic approaches, thanks to easy accessibility of the oral cavity. Until recently, however, only a few topical formulations were considered specific for the treatment of oral mucosal diseases, and most of these were borrowed from dermatology and encumbered by all the inherent limitations associated with these formulations; indeed, the oral cavity has structural, environmental, and functional features that differ from the skin. In particular, the presence of saliva in association with swallowing, chewing, and phonation acts to wash away most of the drug from the site of application, resulting in a short retention time of the dosage forms and, consequently, low therapeutic efficacy.

For these reasons, innovative drug dosage forms for local oral drug delivery should be able to overcome the following various drawbacks:

1. rapid drug loss from the site of absorption by salivary scavenging and mechanical stress;
2. the non-uniform distribution of drugs in saliva on release from delivery systems, which implies that certain areas of the oral cavity might not receive therapeutic levels of drugs;

3. poor patient compliance because of an unpleasant taste and sensation in the mouth;
4. the relative permeability of the oral mucosa and potential barrier region to drug absorption.

In this review, we examine the structure and permeability function of the oral mucosa, the rationale of oral local drug delivery, and new potential bioadhesive local delivery systems.

A comprehensive search of the literature was conducted in Medline and Embase databases, using the key words *oral mucosa, transmucosal drug delivery, buccal drug delivery, buccal tablets, buccal films, buccal patches, buccal gels, and mucoadhesive, polymers* combined separately with the terms *oral cavity, oral lesions, recurrent aphthous stomatitis, oral ulcers, oral lichen planus, oral herpes simplex, oral cancer; vesiculo-bullous diseases, oro-facial pain, salivary dysfunctions, oral candidiasis, radio-chemotherapy-induced oral mucositis and periodontal diseases.*

Oral mucosa: structure and permeability features

The oral mucosa has a total surface area of about 200 cm² and it consists of 2 anatomical and functional layers¹: a thick, stratified squamous avascular epithelium, and an underlying, slightly vascular layer of mesodermal origin (the chorion or lamina propria) (Figure 1). The epithelium of the oral mucosa is approximately 40 to 50 cell layers thick,² with the thickness depending on the site (Table I). Oral squamous stratified epithelium is divided into nonkeratinized and keratinized epithelium. The differentiation processes that occur in keratinized and nonkeratinized epithelia differ significantly, and this results in either the presence or absence of a cornified surface layer. It is noteworthy that there are 3 different types of oral mucosa within the oral

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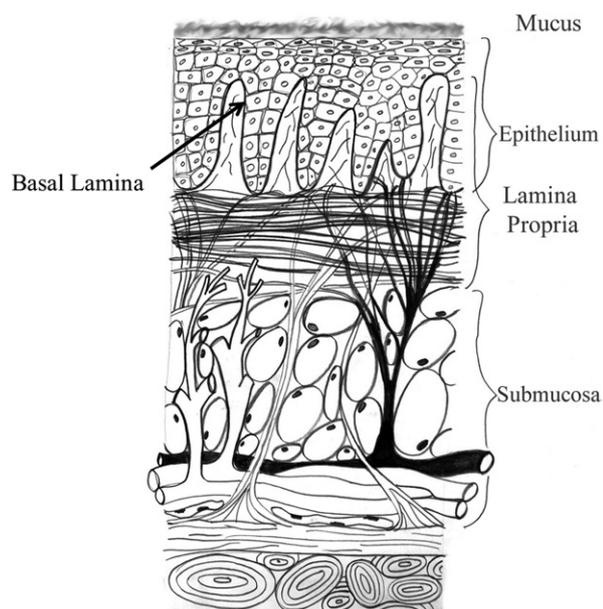


Fig. 1. Structure of the oral mucosa.

Table I. Regional variation in epithelial thickness and permeability pattern within oral mucosa

Tissue	Structure	Epithelial thickness, μm	Permeability
Buccal	NK	500–600	—
Sublingual	NK	100–200	—
Gingival	K	200	—
Palatal	K	250	—

++, very suitable; —, means least suitable; NK, nonkeratinized, K, keratinized.

cavity: masticatory mucosa (i.e., gingivae and the hard palate), specialized mucosa (i.e., the dorsum of the tongue), and lining mucosa (e.g., buccal mucosa, the floor of mouth), representing 25%, 15%, and 60% of oral mucosa, respectively.¹

Knowledge of the permeability features of oral mucosa is crucial in selecting the most appropriate formulation so that a drug is absorbed and it reaches the deeper layers of the oral epithelium, according to local variations in mucosal thickness, epithelial keratinization, and lipid composition. These are collectively known as *barrier region* features. It is generally accepted that the connective tissue of oral mucosa is not an effective barrier to the penetration of substances.³ It has been suggested that there may be 2 sites at which mucosal barrier function may occur.⁴ One of these is localized at the basal complex, and the second is in the intercellular spaces of the superficial epithelial layers. The basal lamina of buccal epithelium may be only marginally responsible for the barrier function; it may limit the passage of certain particles, such as immunocomplexes,⁵ and the rate of penetration of polar sub-

stances owing to the charge on its components; however, the structure of the basal lamina is insufficiently dense to exclude even relatively large molecules. Consequently, there is considerable evidence that the only real barrier to the penetration of polar and nonpolar substances is situated in the upper one-third to one-quarter of the oral epithelium.

Ultrastructural evidence regarding the location of the barrier region in oral epithelium has been obtained from several experiments, demonstrating an increase in permeability when the superficial layers have been removed by stripping.⁶ Further studies have been carried out using several tracers, such as horseradish peroxidase,^{7–9} an enzyme with a molecular weight of 40,000 Da and a length of 5 to 6 nm, and lanthanum nitrate,¹⁰ an electron-dense marker, which is 2 nm in size. These tracers, when placed onto the outer surface of the epithelium, penetrate only a few of the outermost layers. When applied to the submucosal surface, however, they appear to permeate up to the uppermost third of the cell layers of the buccal epithelium. These patterns of penetration are obtained for both keratinized and nonkeratinized epithelia.

Consequently, the barrier region can be considered as being strictly related to the chemical characteristic of the intercellular substances in the superficial layers, especially during the epithelial differentiation process. The permeability barrier of the oral mucosa is primarily attributable to intercellular materials derived from the so-called membrane-coating granules (MCGs), which are found in the intermediate cell layers of both keratinized and nonkeratinized epithelia^{11,12} (Figure 2, A).

Permeability measurements have suggested that different substances may permeate oral epithelium at different rates, depending on the chemical nature of the molecule and the histologic features of the tissue being traversed. There are considerable regional differences in the permeability pattern of the oral mucosa. In general, the permeability of oral mucosa decreases gradually from the sublingual through to the buccal and palatal mucosa.¹³ This rank order is related to the relative thickness and degree of keratinization between these regions: the sublingual mucosa is relatively thin and nonkeratinized, the buccal mucosa is thicker and nonkeratinized, and the palatal mucosa is intermediate in thickness and it is keratinized.¹⁴

Compounds with different chemical properties penetrate the barrier region via different routes. Substances can be transported across the mucosal membrane by passive diffusion, carrier-mediated active transport, or endocytosis.¹⁵ Two main pathways seem to be implicated in passive diffusion across membranous tissues, however: the intracellular (or transcellular) pathway, and the intercellular (or paracellular) pathway (Figure

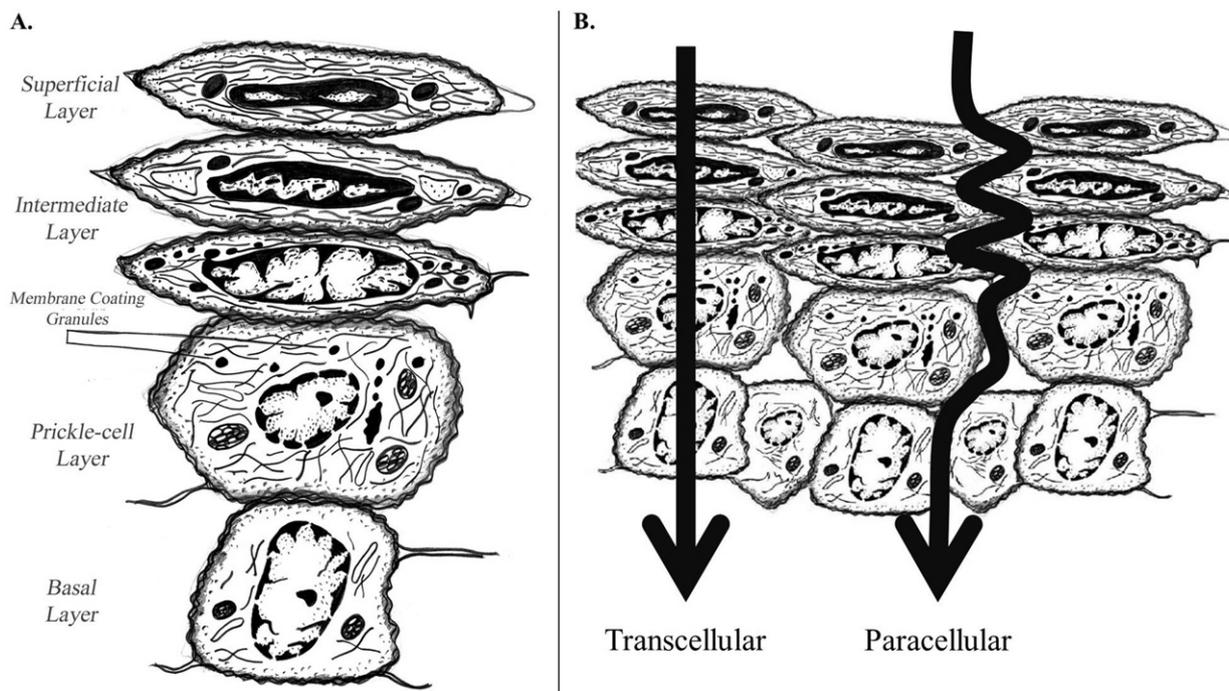


Fig. 2. **A**, Ultrastructural features of oral buccal epithelium. MCGs become evident microscopically in the prickle cell layer, approximately at the midpoint of the epithelium. **B**, Routes of drug transport across oral epithelium.

2, B). A single drug can permeate through oral mucosa, using both routes simultaneously, but the route offering the least resistance to penetration is usually preferred, depending on the physicochemical properties of the drugs (e.g., size, lipophilia, hydrogen bond potential, charge, and conformation).¹⁶

Knowledge of the permeability features of the oral mucosa is critical in assessing the site of drug delivery to ensure a more targeted local effect or a transmucosal systemic effect. Each therapy requires distinct penetration and drug-retention profiles to optimize treatment and minimize side effects.¹⁷ Areas of mucosal pathology, such as erosive, ulcerated, or hyperkeratosis lesions, inevitably decline in mucosal barrier function and this may lead to an increase in the drug's ability to diffuse into the oral mucosa. Indeed, higher permeability values of nitroso normicotine in leukoplakic sites and their surrounding areas than those in normal oral mucosa have been reported in a recent study.¹⁸

Local oral drug delivery

Drug delivery via the oral mucosa can be subdivided into 2 different approaches: drug delivery via keratinized mucosa, and drug delivery via nonkeratinized mucosa (Figure 3). The selection of one approach over another mainly depends on regional differences in terms of anatomic and permeability features, which exist between these oral mucosal sites. The keratinized mucosa, such as gingival and hard palatal mucosa, are

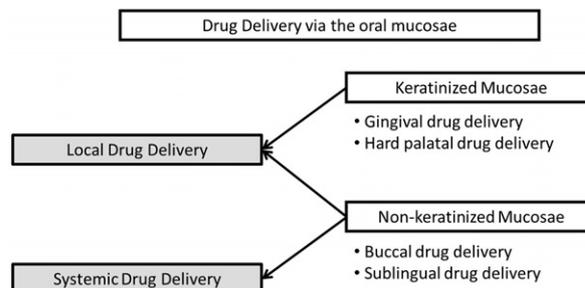


Fig. 3. Drug delivery via the oral mucosae: a schematic representation of possible approaches.

still not considered a valid site for the systemic administration of drugs, and they should be considered as useful sites for local (direct) drug delivery only in treating oral diseases localized at the gingiva or palate. In particular, the rationale behind gingival drug delivery is that concentrated amounts of active drugs can be delivered to the precise site of the disease process with a minimal systemic uptake of the medication. Such devices could be useful adjuncts to conventional mechanical therapy and they are generally associated with low side effects and drug interactions.

Drug delivery via the nonkeratinized mucosa can be subdivided into 2 approaches: sublingual drug delivery (which is the systemic delivery of drugs across the mucosa lining the floor of mouth) and buccal drug delivery (mainly via the buccal mucosa lining the

cheeks, including systemic and/or local delivery). The sublingual mucosa is more permeable and thinner than the buccal mucosa, thus making it a feasible site if a rapid onset is desired. Thus, the sublingual route is generally used for the systemic delivery of drugs in treating acute disorders. The buccal mucosa is considerably less permeable than the sublingual mucosa, and it is unable to provide the rapid onset of absorption observed with sublingual administration.¹³ For these reasons, buccal mucosa constitutes a preferred route for the systemic treatment of chronic disorders when the sustained delivery of systemically acting drugs is required, thereby overcoming the drawbacks when they are administered by conventional routes.¹⁹

Oral local drug delivery consists of a more efficient drug-delivery approach than systemic delivery for the treatment of oral conditions. Many oral diseases are chronic and, hence, require chronic treatment regimens. In addition, most oral diseases can be treated locally, without the need for ingestion and the systemic distribution of drugs. Thus, local drug delivery provides a more targeted delivery, as smaller amounts of drug can be easily targeted at the site of the disease, thereby reducing side effects; however, the oral mucosa has a small surface area and limited exposure times.²⁰ Furthermore, undesirable taste sensations, especially during long-term treatment, could restrict the value of this route of administration. On the basis of these considerations, local drug delivery should be considered a delivery route appropriate for drugs exhibiting high therapeutic potency, as only a relatively small quantity of drug can be delivered.

Mucoadhesive dosage forms

Conventional dosage forms are not capable of releasing medication at a fixed rate to a specific site of action. The main disadvantage is the low bioavailability, which depends on the physiological removal mechanisms of the oral cavity (the washing effect of saliva and mechanical stress). These dosage forms are constantly washed away, resulting in retention times of insufficient duration, unpredictable distribution of the drug on the site of action/absorption, and an initial burst effect, followed by a rapid decrease in concentrations to below therapeutic levels. For these reasons, new *attached* or *adhesive* drug delivery systems for local drug delivery have been developed. These systems offer several advantages over nonattached systems, including intimate contact between the drug dosage form and oral mucosa; extended retention time, without interfering with physiological activities, such as eating, speaking and drinking; and drug release (locally or systemically) at a fixed rate to a specific site of action.

Mucoadhesive dosage forms are a new type of formulation design, able to meet all the previously mentioned requirements. In the early 1980s, Ishida et al.²¹ were the first to pioneer bioadhesive drug delivery systems for administering insulin across the buccal mucosa in beagle dogs. Bioadhesion mechanisms and methods of evaluation have been reviewed by Peppas and Buri.²² Mucoadhesion is a complex phenomenon and several steps have been suggested in mucoadhesive bond formation.²³ The first step is the spreading, wetting, and dissolution of mucoadhesive polymer at the interface. The second step is the mechanical or physical entanglement between the polymer and the tissue surface mucus layer, resulting in an interpenetration layer. The next step is the result of chemical interactions, such as covalent and ionic bonds, hydrogen bonding, and Van der Waals' interactions. Hydrogen bonds and hydrophobic interactions are the most desirable in developing mucoadhesive systems, as strong primary bonds (e.g., covalent bonds and ionic bonds) could cause irreversible damage of the mucosal surface. Park and Robinson²⁴ examined a large number of polymers for their bioadhesive potential and to obtain relevant information regarding the structural requirements for bioadhesion. The dependence of mucoadhesion on pH and carboxyl-group density suggests that mucoadhesion occurs through hydrogen bonding. In addition, the density of the cross-linking agent significantly affects mucoadhesion. To enhance the intrinsic mucoadhesive properties of a polymer, new formulated buccal dosage forms can be composed of several different mucoadhesive polymers and novel copolymers, rather than using single polymeric systems.²⁵⁻²⁸

Dosage forms

According to the mechanism by which a drug is released from the delivery device, dosage forms can be classified into the following categories: a monolithic (or "matrix") type, and reservoir (or "membrane-controlled") type. In the former, the drug is uniformly dispersed or dissolved in the polymer matrix and drug release is effected by diffusion through the polymer network. In the latter, a drug reservoir is entrapped between an impermeable backing layer and a polymeric membrane that controls the rate of drug release (Figure 4, A and B).

The desirable attributes of an oral adhesive system are a high drug-loading capacity, nonirritancy of the tissue, good mucoadhesion, sufficiently reduced dimension, and physical flexibility to be acceptable (in terms of comfort) to the patient, tasteless, and sustained drug delivery.²⁹ Erodible (degradable) formulations can be useful because they do not require system retrieval at the end of the application.

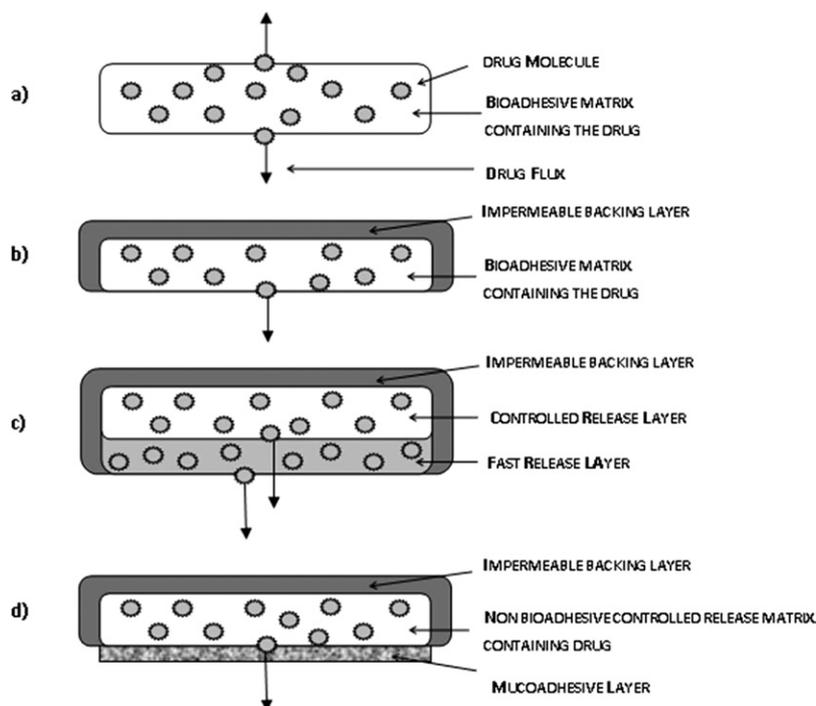


Fig. 4. a-d. Schematic representation of some adhesive buccal drug delivery systems; a) matrix-type delivery device: the most simple kind of delivery systems where drug is uniformly dispersed into the polymeric matrix; b) dosage form with an impermeable backing layer in order to provide the unidirectional release of drugs; c) dosage form characterized by two layers from which drugs could be delivered at different release rate (fast and controlled release) and d) a typical mucoadhesive dosage form with an impermeable backing layer and a polymeric matrix where drug is dispersed or dissolved.

Mucoadhesive systems for oral local drug delivery include adhesive tablets, adhesive patches, adhesive films or pellicles, adhesive semisolid systems (gels, ointments), and adhesive liquid systems (sprays, mouthwashes). Table II summarizes the main mucoadhesive delivery systems for the local treatment of oral diseases.

Adhesive tablets

Several bioadhesive tablet systems have been the subject of growing interest in treating oral diseases.⁶⁶⁻⁶⁹ Buccal tablets are small, flat, and oval with an approximate diameter of 5 to 8 mm and thickness of about 2 mm.⁷⁰ In the presence of saliva, they adhere to the mucosal surface until dissolution and/or drug release is complete. After being in the mouth for a short period, the patient is usually no longer aware of its presence, allowing him or her to speak, drink, and eat without discomfort. Adhesive buccal tablets can be applied to different sites in the oral cavity, including the palate and the mucosa of the cheeks. Recently, mucoadhesive tablets containing chlorhexidine were designed to swell and form a gel, adhering to the mucosa and controlling the drug release into the oral cavity.⁷¹

To prevent drug loss from the top surface of the dosage form, specialized tablets with 2 layers have

been developed. They contain a drug-loaded bioadhesive layer and an impermeable backing layer to promote unidirectional drug absorption and to minimize drug leakage in the oral cavity (Figure 4, B). Several investigators have reported the development of mucoadhesive drug-delivery devices containing both a fast-release and a controlled-release layer^{72,73} (Figure 4, C). Bioadhesive tablets, in which the drug can be released only from the surface of the tablet in contact with the buccal mucosa, have been developed. The other surfaces of these bioadhesive tablets are coated with water-impermeable hydrophobic substances (e.g., ethyl cellulose or oil). Bilayered adhesive tablets containing nystatin have been designed to potentially treat oral candidiasis.⁷⁴

This type of dosage form can be used only for the treatment of localized oral lesions because its main disadvantage is the lack of the physical flexibility of the material applied to the mucosa. This results in a high level of patient discomfort and poor compliance, especially in cases of long-term therapy and/or repeated use. Furthermore, the tablets should not be moved once in position because their separation from mucosal surface causes more rapid drug release, in addition to the possibility of swallowing the device and its inadvertent adhesion to the mucosal surface of the esophagus.

Table II. Most common oral mucosal diseases and novel developed formulations and therapeutics: most dosage forms listed are represented by adhesive semisolid or liquid systems

<i>Drugs</i>	<i>Dosage forms</i>	<i>Results</i>	<i>References</i>
Potentially malignant disorders and oral cancer			
5-FU	Matrix tablets	Matrix tablets containing 5% of 5-FU could be a useful means in topical treatment of OSCC	30
Acitretin	Mucoadhesive 2-layer tablets	Efficacy in the treatment of oral leukoplakia without side effects	31
Tretinoin	Patch	The tretinoin patch is safe and effective for such chemoprevention in the hamster model	32
Ketorolac	Oral rinse	Local delivery of a COX-containing oral rinse was well tolerated but produced no significant reduction in the extent of leukoplakia	33
Black raspberry anthocyanins	Bioadhesive gel	Reversing or down-grading oral dysplastic lesions	34 35
Photosensitizing agents (5-aminolevulinic acid)	Gel	Followed by photodynamic therapy, a complete response was obtained in 10 of 12 treated patients	36
Idarubicin	Solid lipid nanoparticles	Data confirm nanoparticle internalization by OSCC cells and support the premise that nanoparticle-based delivery provides higher final intracellular levels relative to bolus administration	37
Engineered adenovirus	Oral rinse	Some complete response, most transient	38
Imiquimod	Bioadhesive patch	In vitro study that showed a potential clinical use of imiquimod to the treatment of neoplastic conditions of the oral cavity and cervix, as well as the vulva.	39
Oral mucositis			
TGF-β3	Oral rinse	TGF-β3 penetrate the epithelium and is detected in the basal cell layer at therapeutically effective concentrations	40 41
TGF-β3	Chitosan gel	Improved drug retention, protection against Candida infection; bioadhesive gel could act as protective barrier to reduce discomfort	64
Keratinocyte growth factor	Adhesive gel	Tropical prevention and treatment of mucositis. Actually drug is administered systemically	42
Association of a pool of collagen precursor amino acids combined with low molecular weight sodium hyaluronate	Spray	Fast reduction of the pain and clinical amelioration of the lesions	43
Gengigel; Gelclair; MuGard	Mucoadhesive covering agents	Physical coating and protection for thinned or ulcerated oral mucosa	65
OLP			
Clobetasol	Mucoadhesive gel	The application of mucoadhesive tablet containing 24 μg clobetasol 3 times a day appeared to be effective, avoiding the side effects of the generally used treatment	44
Cyclosporin	Mucoadhesive gel	Cyclosporin gel gives stable results when therapy ends in the treatment of OLP	45
Tacrolimus	Oral rinse	There is need for larger placebo-controlled, randomized studies with carefully selected and standardized outcome measures	46
HA	Mucoadhesive gel	Topical HA (0.2%) does appear to be of some benefit in the management of erosive lichen planus	47
Oral infections			
Metronidazole	Mucoadhesive tablets	Tablets performed 12-h drug sustained release for treatment of periodontal disease	48
Miconazole	Mucoadhesive buccal slow release tablet	Has shown more efficacy than conventional topical antifungal agents	49
Tetracycline	Mucoadhesive patch	Combination of tetracycline and carvacrol showed excellent activity against <i>Candida albicans</i> . The prepared patches showed a sustained release action for more than 6 h, acceptable bioadhesion, and stability	50

Table II. Continued

<i>Drugs</i>	<i>Dosage forms</i>	<i>Results</i>	<i>References</i>
Salivary hypofunction and xerostomia			
Physostigmine	Long-lasting gel	Locally applied gel relief in the feeling of dryness	51
Interferon alfa	Tablets	Enhance salivary secretion in patients with primary Sjögren syndrome	52
Recurrent aphthous stomatitis			
Amlexanox	Mucoadhesive tablets	Efficacy and safety in reducing aphthous ulcer pain and lesion size	53
Amlexanox	Adhesive patches (OraDisc)	Efficacy in the prevention and treatment of oral ulcerations	54
Amlexanox	Oral adhesive pellicles	Better flexibility, higher compliance and patient comfort, but same clinical efficacy in comparison with adhesive tablets	55
HA	Mucoadhesive gel	Efficacy and safety in reducing size, number and symptoms of oral ulcers	56
			57
Doxycycline	Mucoadhesive gel	Faster reduction in pain during than the placebo group	58
Periodontitis/Peri-implantitis			
Chlorhexidine, doxycycline, minocycline, satranidazole or metronidazole	Mucoadhesive gels	Improvement in probing depths and attachment levels	59
			60
			61
			62
Minocycline	Microspheres	In association to mechanical treatment favor an improvement of probing depth in cases of peri-implantitis	63

5-FU, 5-fluoruracil; COX, cyclooxygenase; HA, hydroxyapatite; OLP, oral lichen planus; OSCC, oral squamous cell carcinoma; TGF-β3, transforming growth factor beta-3.

Adhesive patches and films

Laminated patches and films are the most recently developed dosage form for buccal administration. These drug-delivery approaches are promising not only for systemic drug release.^{64,75} The first step in the development of this adhesive dosage form is the selection and characterization of a polymer (or combination of polymers) with appropriate bioadhesive properties and drug-release control, so as to obtain both of these properties.^{76,77} Bioadhesive patches and films are laminates, consisting of a polymeric drug-loaded layer, an impermeable backing layer, to promote unidirectional drug release and, generally, mucoadhesive components with or without release retardants and additives, such as penetration enhancers or enzyme inhibitors.²¹ Anders et al.⁷⁸ investigated a number of polymers and different geometries for developing patches and films for the delivery of different peptides. Despite long manufacturing times and high costs, the characteristics of oral patches and films make them a suitable dosage form for the direct treatment of localized and mild diffuse oral diseases. Oral patches and films have high flexibility, thus facilitating a long residence/retention time, in addition to a high level of patient compliance and comfort. Furthermore, they provide a more accurate dosing of drug delivery, compared with other dosage forms, such as gels and sprays. Finally, these adhesive dosage forms, thanks to their flexibility and good retention time, protect the underlying diseased tis-

sues, thus reducing pain and increasing treatment effectiveness.

In our opinion, mucoadhesive patches should be preferred to adhesive tablets in developing new drug-delivery systems for oral local drug delivery. Furthermore, oral films could be useful in the treatment of mild or severe diffuse oral diseases, in particular chronic oral diseases where long-term drug regimens are often required, because of their high retention time and increased patient comfort.

Adhesive semisolid systems (gels, ointments)

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. They form an intimate contact with the mucosal membrane and rapidly release drug at the absorption site⁷⁹; however, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention time of the gels at the site of application has been overcome by using bioadhesive formulations. Nevertheless, despite the use of bioadhesive polymers, the residence time of gels is small because body fluids, such as saliva, will quickly wash them away from the site of action. For these reasons, they are of limited use for drugs with a narrow therapeutic window. Bioadhesive gels for application on oral mucosa in the treatment of some oral diseases have been known for many years. A major application

of adhesive gels could be the local delivery of medicinal agents for the treatment of periodontitis, recurrent aphthous stomatitis, traumatic ulcers, radiation- or chemotherapy-induced oral mucositis, chronic immunologically mediated oral lesions, hyposalivation, and, recently, for the healing of wounds.

Adhesive liquid systems (oral rinse and sprays)

Adhesive liquid systems produce a very fine mist, which tends to coat the entire oral mucosa, thereby increasing the total surface area through which drug molecules can be absorbed. Compositions possessing high mucoadhesion and viscoelasticity have been suggested for the treatment of oral mucosal disease by virtue of their film-forming properties. Bioadhesive liquid systems (oral rinse and sprays) have been proposed for the treatment of several oral diseases, such as oral lichen planus and other immunologically mediated diseases, aphthous stomatitis, oral mucositis, hyposalivation and potentially malignant disorders, such as leukoplakia and erythroplakia.⁶⁵ An ideal adhesive spray system should be able to produce sprays patterns of a suitable ovality and particle size. The ovality of the spray pattern refers to the symmetric oval shape of spray particles. In general, it is believed that the more the oval shape of spray particles is symmetric, the greater will be the ability of the particles to cover the whole mucosa. Furthermore, a spray drug-delivery system should provide a suitable behavior so as to be delivered in an appropriate unit dose volume, by avoiding unintended administration through the gastrointestinal tract by swallowing.⁸⁰

CONCLUSIONS

Currently, many biologically active drugs for the treatment of oral conditions have been administered systemically with possible serious side effects that limit their use only to severe and refractory cases. The development of effective systems for local drug delivery could be very interesting in providing a more targeted therapeutic option, thereby reducing the required drug doses and the risk of systemic side effects. One important outcome for this new approach could be the possibility of providing more effective treatment regimens to a wider range of patients also suffering from severe or refractory oral diseases. Furthermore, novel macromolecular biological drugs, such as antibody-based drugs, could be suitable medications to be administered by local delivery systems, in particular, those used for the treatment of chronic immunologically mediated oral diseases, without the need for a systemic administration regimen. However, the relative impermeability of the oral cavity, other variables pertaining to the oral environment (e.g., eating and the effects of saliva), and

acceptability by the patient must be considered in developing new dosage forms. The development of new formulations for topical drug delivery within the oral cavity is a research field that should be intensively investigated, considering the high prevalence of oral mucosal lesions and periodontal disease and their negative impact on patients' quality of life.

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