Bioadhesive Drug Delivery Systems

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Chapter 6

MUCOADHESIVE BUCCAL PATCHES FOR PEPTIDE DELIVERY

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I. INTRODUCTION

Due to an increasing supply of potent peptide and protein drugs, the biopharmaceutical sciences are presently faced with an urgent need to develop alternative dosage forms for nonparenteral absorption. Among the nonparenteral sites suitable for administering peptides and proteins are the mucosae of the nasal, buccal, vaginal, rectal, and even ocular routes. The currently most popular site is the nasal pathway. According to various reports, e.g., reviewed by Su and Campanale[1] and Su et al.,[2] it represents the route of choice, mainly because of its superior permeability to peptides as compared to the other mucosal sites.

However, the nasal site does have distinct limitations. Upon long-term treatment, there might be a risk for pathologic changes of the nasal mucosa;[2] the drug or a preservative added to the preparation might interfere with the ciliary activity of the membrane, as shown by Van de Donk and co-workers.[3] Moreover, there is a debate on the consequences of vast individual variations in mucus secretion and turnover on the extent and rate of nasal absorption; in addition, proteases and peptidases present in the mucus or associated with the nasal membrane may act as a dense enzymatic barrier to peptide absorption.[4,5] It may thus be concluded that in spite of many promising aspects the nasal route may have its shortcomings and not be the only answer to peptide absorption problems.

Information on the buccal absorption of peptides is still rather scarce, except for a broad body of knowledge on the buccal absorption of oxytocin, e.g., by Wespi and Rehsteiner,[6] Bergsjö and Jenssen,[7] and Sjöstedt,[8] dating back to the 1960s. Moreover, for many conventional drugs, the oral mucosa has been an established absorption site. Recently more peptides were investigated, and it was shown that the buccal mucosa might provide a useful absorption site, mainly restricted to small peptides.[9-14] Data are also available for vasopressin analogs and insulin.[15-17] However, as compared to other alternative peptide absorption sites, such as the rectal, nasal, and vaginal mucosa, much less information is available for the oral mucosa.

In terms of permeability, in addition to the nasal mucosa, even the rectal and the vaginal mucosae seem to be preferable to the buccal site. On the other hand, what makes the oral mucosa, mainly the buccal, the labial, and the sublingual sites rather attractive for peptide delivery is the combination of several aspects:

- Excellent accessibility
- High patient acceptance and compliance
- Significant robustness of mucosa

Because of the excellent accessibility of the oral mucosa, appropriate dosage forms can

be easily attached and removed at any time, if necessary. Moreover, application is usually painless and without significant discomfort whatsoever. Since patients are well adapted to the oral administration of drugs in general, the acceptance of buccal or sublingual dosage forms should be good, and there should be a high compliance as well. According to its natural function, the oral mucosa is routinely exposed to a multitude of different foreign compounds and, therefore, is supposed to be rather robust and less prone to irreversible irritation or damage by the drug, the dosage form, or the additives, e.g., absorption promotors, used therein. In addition, there is no sex-specificity involved as with the vaginal absorption. Moreover, nasal and vaginal secretions and mucus flow are subject to rather pronounced variations, both in qualitative as well as quantitative terms. On the other hand, with respect to proteolytic enzymes present in the mucosal membrane or fluid there is no principal difference or advantage of the oral mucosa in comparison to the other sites.

Therefore, in spite of the undoubtedly higher natural permeability of the rectal, the vaginal, and especially the nasal mucosa, the buccal route appears to be a rather attractive one, but appropriate dosage forms have to be provided, and efficient absorption promotors should be found to increase its permeability.

II. RELEVANT ANATOMY AND PHYSIOLOGY OF THE ORAL MUCOSA

The oral cavity is lined by a relatively thick, dense, and multilayered mucous membrane of a highly-vascularized nature. Drug penetrating into the membrane can find access to the systemic circulation via nets of capillaries and arteries. The arterial flow is supplied by branches of the external carotid artery. The venous backflow goes via capillaries and a venous net is finally taken up by the jugular veins. The equally well developed lymphatic drainage runs more or less parallel to the venous vascularization and ends up in the jugular ducts.

As compared to the relatively thin nasal mucosa with only a few cell layers to be penetrated before uptake by the systemic circulation takes place, the oral mucosa with its multilayered structure appears to be much more resistant against penetration of drugs.

The epithelium of the oral cavity is in principle similar to that of the skin, with interesting differences regarding keratinization and the protective and lubricant mucus spread across its surface. The total area is about 100 cm.[2,18] The buccal part with about one third of the total surface is lined with an epithelium of about 0.5 mm thickness, and the rest by one of 0.25 mm thickness.[19] The multilayered structure of the oral mucosa is formed by cell divisions, which occur mainly in the basal layer. As reviewed by Jarrett,[20] the mucosa of the oral cavity can be divided into three functional zones. First, the mucus-secreting regions (consisting of the soft palate, the floor of the mouth, the under-surface of the tongue, and the labial and buccal mucosa) have a normally nonkeratinized epithelium. These regions are supposed to represent the major absorption sites in the oral cavity. Second, the hard palate and the gingiva are the regions of the masticatory mucosa and have a normally keratinized epidermis. Third, specialized zones are the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

An important feature of the oral mucosa as a mucous membrane is the turnover of the cells, which is definitely greater — ranging from 3 up to 8 days for a complete turnover — than that of the skin epidermis (ca. 30 days). This is because of the constant replacement of the nonkeratinized or partly keratinized cells, which is necessary to stabilize function and integrity of the mucosa. A reduction of the mucosal mitotic activity would result in a loss of epithelial continuity.[20]

Keratinization and average size of the epithelial cells seem to have an inverse relationship. The mean cross-sectional area of the cells of the cheek is about 263 μm^2, while it is about

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