EXHIBIT 3

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Evaluation of laminated muco-adhesive patches for buccal drug delivery

Reinhold Anders * and Hans P. Merkle

Pharmazeutisches Institut, Pharmazeutische Technologie, Universität Bonn, Bonn (F.R.G.)

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Summary

The aim of this study is the development and evaluation of adhesive patches for buccal administration, consisting of two-ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The patches were prepared by a casting procedure using viscous aqueous solutions of drug and hydrocolloid polymers, and subsequent drying. The polymers used were hydroxyethylcellulose, hydroxypropylcellulose, poly(vinylpyrrolidone) and poly(vinylalcohol). The integrity of the laminate is based on adhesive bonds between the hydrocolloid layer and an agarose layer grafted to one side of the backing layer sheet. After mucosal contact, firm adhesion to the mucosal surface is established by interactions of the swollen polymer and the buccal mucus layer. The duration of mucosal adhesion in vivo is affected by the type of polymer used, its viscosity grade, the polymer load per patch, and the drying procedure for preparation. A wide range of drug release rates can be achieved by varying these parameters. Drug release rates are controlled by polymer dissolution kinetics.

Introduction

Drug absorption via the mucosal epithelium of the oral cavity is an established route of drug delivery, which is especially useful if peroral absorption is incomplete or ineffective, e.g. with drugs undergoing strong first-pass effects after ingestion, and with peptide drugs being digested upon gastrointestinal transit. Oral mucosal application is also supposed to show a more rapid absorption than the peroral pathway. A variety of drugs have been shown to be absorbed, mainly by the buccal, the sublingual or the gingival mucosa, whereas the palatal mucosa and the mucosa of the tongue were assumed to be less permeable (Jarrett, 1980). Even peptide drugs were found to pass the oral mucosae (Wespi and Rehsteiner, 1966; Earle, 1972; Laczi et al., 1980; Ishida et al., 1981; Anders et al., 1983; Schurr et al., 1985), at least to some extent.

In terms of peptide permeability, other mucosal epithelia appear to be more efficient than the oral mucosa, e.g. the nasal, vaginal and rectal mucosae. On the other hand, what makes the oral mucosa rather attractive for peptide delivery, is a combination of several aspects: (i) The oral mucosa is easily accessible, so dosage forms can be easily administered and even removed from the site of

* *Present address*: Hoechst AG, D-6230 Frankfurt a.M. 80, F.R.G.
Correspondence: H.P. Merkle, Institut für Pharmazeutische Technologie der Universität Frankfurt, Georg-Voigt-Str. 16, D-6000 Frankfurt, Federal Republic of Germany.

application. (ii) Since patients are well adapted to the oral administration of drugs in general, patient acceptance and compliance is expected to be good. (iii) According to its natural function the oral mucosa is routinely exposed to a multitude of different external compounds and, therefore, is supposed to be rather robust and less prone to irreversible irritation or damage by a dosage form, its drug, excipient or additive. So in spite of the undoubtedly higher permeability of other mucosal sites, the oral mucosa appears to be an attractive alternative, providing appropriate dosage forms can be devised.

Delivery of drugs via the oral mucosa by conventional means may be achieved by using solutions or conventional buccal or sublingual tablets or capsules. Large quantities of solutions (≤ 25 ml) may be applied as a mouthwash. Solutions in small quantities (≤ 1 ml) may be filled into capsules with the liquid being released upon chewing. More common dosage forms are erodible or chewable buccal or sublingual tablets and capsules. Due to involuntary swallowing of the dosage form itself or parts of it and due to a continuous dilution of the suspended or dissolved drug by the salivary flow, there is a high risk that a major part of the drug of such dosage forms may not be available for absorption. Moreover, administration of conventional buccal and sublingual tablets and capsules does not go along with drinking and eating and is, at least, a handicap for speaking, so any administration is restricted to rather limited periods of time and controlled release is not within the scope of such formulations.

As a consequence, adhesive mucosal dosage forms were suggested for oral delivery, including adhesive tablets (Davis et al., 1982; Schor et al., 1983), adhesive gels (Ishida et al., 1983a and b; Bremecker, 1983; Bremecker et al., 1983, 1984), and adhesive patches (Ishida et al., 1981, 1982; Anders, 1984; Merkle et al., 1986). Strong adhesive contact to the mucosa is established by using muco-adhesive polymers as excipients.

The laminated patches developed in this laboratory are composed of an impermeable backing layer and muco-adhesive, non-ionic hydrocolloid polymer layers containing the drug. Depending on its size and shape the patch may be administered at different administration sites including the buccal, sublingual and gingival mucosa. Patches administered to the buccal mucosa may have a size of up to about 12 cm^2 at most. Ellipsoid or oval-shaped patches seem to be especially suitable for this site. The sublingual or gingival sites require rather small patches of no more than 1–3 cm^2. For optimum acceptance and compliance of the patches, high flexibility of the patches is required which is a prerequisite for perfect adhesion and prevention of local discomfort.

Due to the impermeable backing layer design there is no excessive wash-out of the drug by saliva, so a maximum drug activity gradient to the mucosa is established. The wash-out of the adhesive is also diminished which minimizes the amount of adhesive necessary to ensure adhesion. In addition to the drug the system may also be loaded with any additive needed. The effect of the additive can be restricted to the very site of adhesion. A local microenvironment may thus be established for more favourable absorption (e.g. by an additive for local pH adjustment, or by a suitable absorption adjuvant). Furthermore, any eventual irritation of the mucosa by the drug or an additive is restricted to the area of the application site. Considering risk and benefit one may tolerate minor local rather than general irritations since the site of application may be varied to allow for regeneration of the tissue.

As is known from the fundamental review of Peppas and Buri (1986), mucosal adhesion is based on the intercalation of hydrated hydrocolloid chains and the glycoprotein chains of the oral mucosa. More recent studies in this laboratory have shown that the force required to separate such bindings can be as high as about 1 $N \cdot cm^{-2}$ in the initial stage of adhesion, which is much more than the force required to ensure safe mucosal adhesion. Due to the gradual dissolution of the polymer the adhesive force then fades out (Wermerskirchen and Merkle, 1988).

The first focus of this report is on the duration of mucosal adhesion in human subjects as a function of the type of polymer used, its viscosity grade, its amount per patch and the drying technique used to prepare the patches. Further data

will concentrate on the release process of protirelin and sodium salicylate (as a marker substance), also performed in human subjects, showing how the release from the patches may be controlled. Finally, information on within- and between-subject variation of buccal release will be given.

Materials and Methods

Materials

The following water-soluble hydrocolloid muco-adhesives were used: hydroxyethyl cellulose (Natrosol 250, Hercules, Hamburg), hydroxypropyl cellulose (Klucel, Hercules, Hamburg), poly(vinylpyrrolidone) (PVP, Kollidon, BASF, Ludwigshafen) and poly(vinylalcohol) (PVA, Mowiol, Hoechst, Frankfurt). Further information regarding molecular weight and viscosity is given in Table 1.

The main backing layer used in this study was Multiphor (sheets; LKB, Gräfelfing). Multiphor sheets were 168–176 μm thick and on one side covered with a thin layer of agarose grafted onto the polymer. This material is commonly used as backing layer for gel chromatography sheets. The material available on the market is rather stiff and not flexible enough to allow comfortable buccal use, so it should be regarded as a model. In some cases cellophane (Cellophane 325 P10; Kalle, Wiesbaden) was taken as the backing layer. According to producer information the thickness of the cellophane in dry state was 22 μm.

Protirelin (TRH) was used as the model peptide drug, and was a gift obtained from Henning (Berlin) and Hoechst (Frankfurt). In addition, sodium salicylate was used as a marker compound and obtained from Merck (Darmstadt). All other chemicals used were of reagent grade.

Preparation of adhesive polymer patches

Preparation of adhesive patches was as follows: given volumes of appropriately made aqueous polymer solutions (for drug-free patches) or drug/polymer solutions (for drug-loaded patches) were cast onto a backing layer sheet mounted on top of

TABLE 1

Molecular weights and specific viscosity of water-soluble hydrocolloids

Polymer	Trade name	Molecular weight [a]	Viscosity [b] (mPa · s)
Hydroxyethylcellulose (HEC)	Natrosol 250 L	80 000	14 (2%)
	Natrosol 250 G	300 000	300 (2%)
	Natrosol 250 K		2 000 (2%)
	Natrosol 250 M	650 000	600 (2%)
	Natrosol 250 H	900 000	30 000 (2%)
Hydroxypropylcellulose (HPC)	Klucel EF (E)	60 000	500 (10%)
	Klucel JF (J)		30 (2%)
	Klucel MF (M)		5 000 (2%)
	Klucel HF (H)	1 000 000	2 000 (1%)
Poly(vinylpyrrolidone) (PVP)	Kollidon 17	9 500	2 (10%)
	Kollidon 25	27 000	4 (10%)
	Kollidon 30	49 000	7 (10%)
	Kollidon 90	1 100 000	500 (10%)
Poly(vinylalcohol) (PVA)	Mowiol 4-88	23 300	4 (4%)
	Mowiol 40-88	114 400	40 (4%)
	Mowiol 4-98	23 300	4 (4%)
	Mowiol 56-98	202 400	56 (4%)

[a] Mean molecular weight as given by the producer.
[b] Viscosity at a given concentration of polymer in water (in parentheses); Brookfield method for HEC and HPC (25 °C), Höppler method for PVP and PVA (20 °C); data as provided by the producer.

a stainless steel plate by means of a frame. Previous to the preparation, the device was carefully rectified in a horizontal position. To ensure constant temperature for drying, the steel plate was constantly perfused by a thermostated stream of water (i.e. contact drying). Drying at 38 °C for about 2 h resulted in a laminate consisting of a backing layer and a hydrocolloid or hydrocolloid/drug layer. By means of a suitable punch–die, the laminate was cut into patches of about 10 cm^2 having an oval form of 4 cm length and 3 cm width. If not otherwise specified this preparation technique was used throughout. For the preparation of PVP and PVA patches 1,2-propylene glycol was used as plasticizer (PVP, 10% (w/w); PVA, 20–25% (w/w) of polymer content). Otherwise the hydrocolloid films became brittle and the laminates disintegrated upon storage.

In some cases, other drying procedures were applied: after careful horizontal rectification and casting of a given quantity of polymer solution, the two-ply laminate was alternatively obtained by drying in a convection oven (i.e. convection drying) at 38 °C (Heraeus, KTG 900, Hanau) or by freeze-drying (Christ, Delta Ia, Aichach-Oberbernbach).

Determination of duration of mucosal adhesion of adhesive patches in vivo

The duration of mucosal adhesion of drug-free adhesive patches was determined in vivo. The same subject was used throughout the study (26-year-old male) if not otherwise specified. A self-adhesive patch was attached to the subject's right or left buccal mucosa and a blank backing layer (as non-adhesive control) on the other side. The size of the patches used was very close to the maximum buccal area available for application, as limited by the local anatomy. The duration of mucosal adhesion was the time span required until the adhesive patch completely lost its adhesive contact with the mucosa. This was assessed by continuing sensual comparison of the behaviour of both patches on either side.

The test requires well-trained and motivated subjects. Three runs were made for each polymer composition. The test sequence was randomised with respect to polymer species and amount of polymer, and the subject was not given information about the polymer composition of the respective adhesive patch tested. During the test the subject was not allowed to drink or eat.

In vivo drug and polymer release from adhesive patches

Drug and polymer (PVP) release profiles were followed by analyzing the amount of drug and/or polymer, respectively, remaining on the patch after given contact times. As drug models, protirelin and sodium salicylate (as a marker compound) were used.

The procedure was as follows. The patches were attached to the buccal mucosa of human subjects, removed after given time periods and analyzed for protirelin or salicylate. Excess saliva on the non-adhesive side of the patch was wiped off with a tissue. Polymer and drug remaining on the patch were dissolved in water under constant stirring for 0.5 h. Protirelin was analyzed by RIA or HPLC, sodium salicylate by UV spectrometry. PVP was analyzed using a modified colorimetric method of Levy and Fergus (1953) (see below).

Analytical methods

UV / VIS spectrometry. Sodium salicylate was directly analyzed at 296 nm. The method to analyze PVP was a slight modification of a procedure previously published by Levy and Fergus (1953). It is based on the formation of a red inclusion complex of iodine in PVP: 4 ml of an aqueous polymer solution containing 10–200 μg PVP/ml were diluted in ca. 15 ml 0.4 M citric acid solution. After adding 2.00 ml of 0.006 M iodine/KI solution and 0.4 M citric acid solution for a final volume of 25 ml the complexed PVP is measured at 420 nm against a blank.

RIA of protirelin. The RIA of protirelin containing aqueous solutions was provided by Hoechst (Frankfurt). The method used was based on previous work by Fraser and McNeilly (1983): the anti-serum was sheep anti-protirelin serum AS-420 1 : 15 000 (Fraser/MRC Reproductive Biology Unit, Edinburgh); the antigen was protirelin/BSA conjugate; specific activity of the tracer was 35–50 μCi/μg; the range of the standard curve was between 7.8 and 2000 ng/sample; relative S.D. within assays was 7.2%, and between assays 11.0%.

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