*International Journal of Pharmaceutics*, 49 (1989) 231–240
Elsevier



IJP 01672

# 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.)*

(Received 28 June 1988)
(Accepted 17 July 1988)

*Key words*: Buccal delivery; Buccal patch; Mucosal adhesion; Laminate; Adhesive polymer; Bioadhesion

## 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 ($\leq 25$ ml) may be applied as a mouthwash. Solutions in small quantities ($\leq 1$ 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 $\mu$m 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 $\mu$m.

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 | 80000 | 14 (2%) |
| | Natrosol 250 G | 300000 | 300 (2%) |
| | Natrosol 250 K | | 2000 (2%) |
| | Natrosol 250 M | 650000 | 600 (2%) |
| | Natrosol 250 H | 900000 | 30000 (2%) |
| Hydroxypropylcellulose (HPC) | Klucel EF (E) | 60000 | 500 (10%) |
| | Klucel JF (J) | | 30 (2%) |
| | Klucel MF (M) | | 5000 (2%) |
| | Klucel HF (H) | 1000000 | 2000 (1%) |
| Poly(vinylpyrrolidone) (PVP) | Kollidon 17 | 9500 | 2 (10%) |
| | Kollidon 25 | 27000 | 4 (10%) |
| | Kollidon 30 | 49000 | 7 (10%) |
| | Kollidon 90 | 1100000 | 500 (10%) |
| Poly(vinylalcohol) (PVA) | Mowiol 4-88 | 23300 | 4 (4%) |
| | Mowiol 40-88 | 114400 | 40 (4%) |
| | Mowiol 4-98 | 23300 | 4 (4%) |
| | Mowiol 56-98 | 202400 | 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%.

*HPLC of protirelin.* HPLC of protirelin was provided by Henning (Berlin). A minor modification of the previously published method of Spindel and Wurtmann (1979) was used: ion pair RP-chromatography of protirelin/1-heptane-sulfonate and UV detection at 210 nm.

## Results and Discussion

*General observations with patches*

The patches used in this study were mainly designed for the buccal delivery of oligopeptides (Anders, 1984; Merkle et al., 1986). But there is no doubt that this type of muco-adhesive patches may be useful for other drugs as well.

Due to the agarose-graft on one side of the backing layer used in the study (Multiphor), there was perfect binding between backing layer and muco-adhesive polymer layer. No disintegration of any patch was ever observed in this investigation, neither in the hydrated nor in the non-hydrated state. On the other hand, the type of backing layer used in the study was not flexible enough to avoid local discomfort for the subjects. This backing layer (Multiphor) is specifically designed to act as a support film for gel-chromatography sheets. Accordingly, with respect to its agarose-graft, Multiphor is regarded a prototype material, ensuring binding between the hydrocolloid and the water-insoluble backing layer both in a hydrated and non-hydrated state. For buccal delivery of drugs similarly coated, more flexible and softer sheets should be used instead.

The use of cellophane as a backing layer turned out to shorten the duration of muco-adhesion of the films. This is due to the rapid penetration of water through cellophane into the hydrocolloid in contrast to the virtually water-impermeable Multiphor sheets allowing water uptake from the mucosal side only.

*Duration of mucosal adhesion of patches*

The patches investigated were two-ply laminates with a drug-free muco-adhesive. The results of a detailed adhesion study with different non-ionic polymers and viscosity grades are given in Figs. 1 and 2. As a result of a previous preliminary

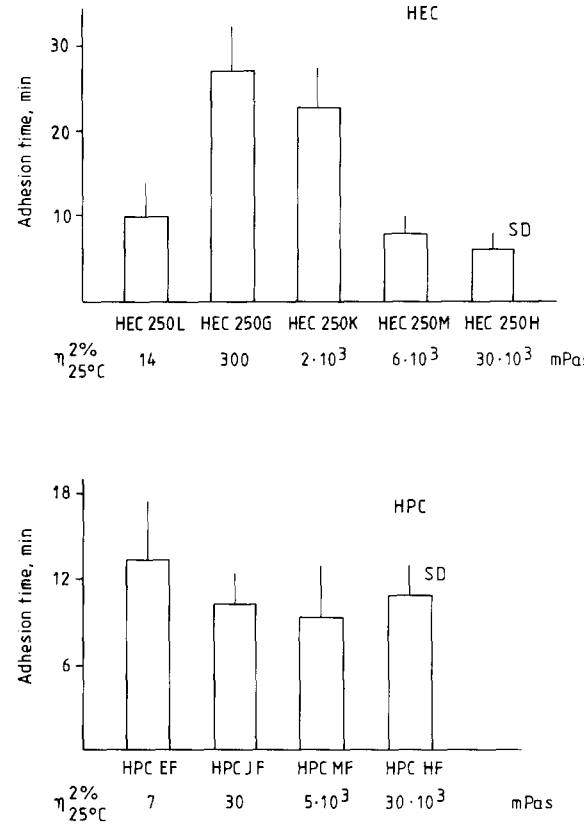


Fig. 1. Effect of viscosity grade of HEC and HPC on duration of mucosal adhesion in vivo. HEC, 2.8 mg·cm$^{-2}$; HPC, 2.9 mg·cm$^{-2}$; backing layer, cellophane. All data in one subject.

screening, it was shown that among the cellulose ethers studied HEC and HPC possess superior mucosal adhesion as indicated by the duration of buccal adhesion in a human subject. Fig. 1 shows that up to 30 min of adhesion was achieved with HEC and up to about 15 min with HPC, at a polymer load as low as 2.8 and 2.9 mg·cm$^{-2}$. With HEC the adhesion duration vs viscosity grade relationship was found to show a maximum. HEC Natrosol 250 G and K proved to be most adhesive. Lower and higher viscosity grades demonstrated less adhesion. It is noteworthy that an inverse relation was found with HPC, showing a minimum of adhesion at medium viscosity grades and increased adhesion at low and high viscosity grades. The mechanism of the inverse relation is not yet clear and will be further investigated.

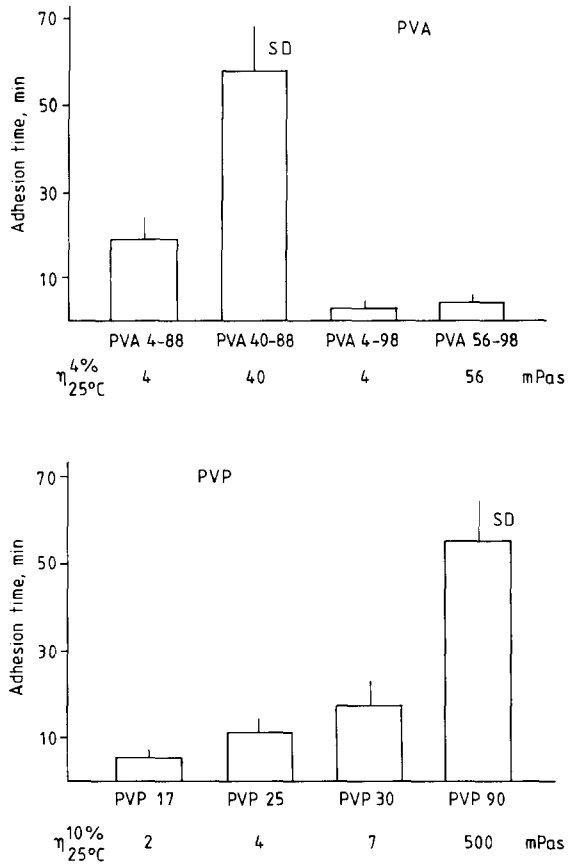


Fig. 2. Effect of viscosity grade of PVA and PVP on duration of mucosal adhesion in vivo. PVA, 17.9 mg·cm$^{-2}$; PVP, 14.9 mg·cm$^{-2}$; backing layer, Multiphor. All data in one subject.

Fig. 2 shows the corresponding results with PVA and PVP. In both cases an increase in viscosity resulted in prolonged adhesion. The adhesion of PVA (Mowiol) patches with the high poly(vinylacetate) (PVAc) content (PVA 4-88, PVA 40-88, corresponding to 12% PVAc), lasted much longer than with the lower PVAc content (PVA 4-98, PVA 56-98, 2% PVAc content). Dissolution of the polymer was complete with PVA 4-88 and PVA 40-88 only; incomplete dissolution was found with both PVA patches of low PVAc content and corresponds to insignificant adhesion (PVA 4-98, PVA 56-98). With PVP (Kollidon), only the highest molecular weight studied showed significant buccal adhesion (PVP 90).

TABLE 2

*Comparison of adhesive properties of different polymers in vivo*

| Polymer/trade name | Amount of polymer (mg·cm$^{-2}$) | Duration of adhesion | | |
|---|---|---|---|---|
| | | Mean | S.D. | *n* |
| HEC/Natrosol 250 G | 2.90 | 32.7 | 5.7 | 3 |
| HPC/Klucel EF | 5.82 | 32.3 | 7.6 | 3 |
| PVP/Kollidon 90 [a] | 8.81 | 36.3 | 8.1 | 3 |
| PVA/Mowiol 44-88 [b] | 8.75 | 30.3 | 6.7 | 3 |

[a] 1,2-propylenglycol as plasticizer, 10% (w/w).
[b] 1,2-propylenglycol as plasticizer, 25% (w/w).

HEC Natrosol 250 G turned out to be the most effective polymer studied. This is exemplified in Table 2 comparing the amounts of polymer per cm$^2$ required to achieve similar durations of mucosal adhesion in the subject. As a potent mucosal adhesive, HEC 250 G was, therefore, used for a series of peptide buccal absorption studies in human subjects and in rats (Anders, 1984; Merkle et al., 1986).

*Effect of drying techniques on adhesive behavior of adhesive patches in vivo*

The effect of different preparation techniques on the adhesive behavior of buccal patches were studied with HEC Natrosol 250 G and PVP Kollidon 90 as polymers. The data are given in Fig. 3. It is demonstrated that the drying procedure ap-

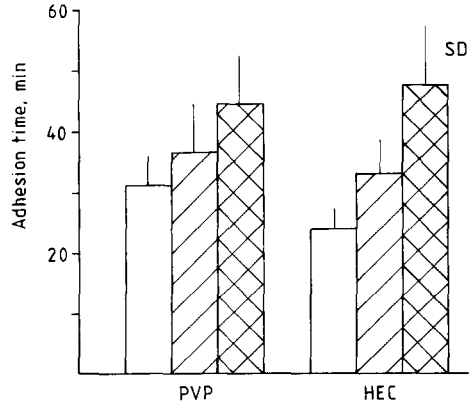


Fig. 3. Effect of drying techniques on adhesive behavior of adhesive patches in vivo. Freeze drying (open), convection drying (hatched), contact drying (double-hatched). HEC 250 G, 3.0 mg·cm$^{-2}$; PVP 90, 8.9 mg·cm$^{-2}$; backing layer, Multiphor. All data in one subject.

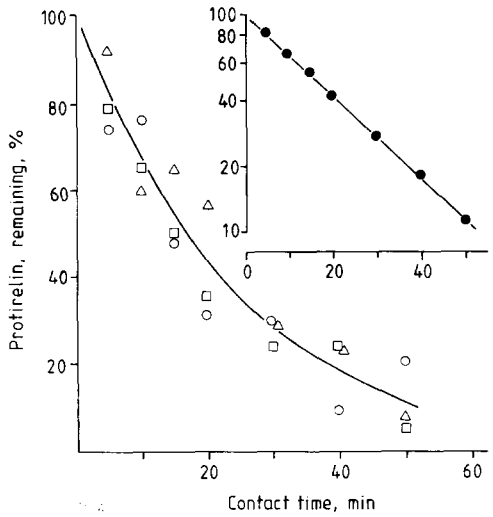


Fig. 4. Typical profile of buccal release of protirelin from adhesive patch; data of three batches (○, □, △); all data in one subject; 2.1 mg·cm$^{-2}$ HEC 250 G, 1.0 mg protirelin per patch; backing layer: Multiphor.

plied to prepare adhesive patches markedly influences the duration of mucosal adhesion in a human subject. For both polymers applied, increasing mucosal adhesion was found in the order of: freeze drying < convection drying < contact drying. This behavior may be due to different densities of the polymeric matrix achieved upon drying and its effect on swelling and dissolution.

*In vivo drug release from adhesive patches*

A typical example for drug release is given in Fig. 4 showing the results of a study (HEC Natrosol 250 G patch, 2.1 mg · cm$^{-2}$) on 3 batches of the same composition in one subject. Each of the data points represents a complete release experiment. The profile indicates exponential drug release (see insert). The variation seen in the graph represents both batch variation and within-subject variation of this dosage form and remains in a reasonable range.

*Effects of polymer, viscosity grade of polymers and polymer loads on in vivo release from patches*

The experiments were performed with sodium salicylate (as a marker substance) loaded patches (10 mg per patch) using different polymers, viscosity grades and polymer loads. All experiments were run in one subject.

The release profiles of the marker are demonstrated in Figs. 5 and 6. It is clearly shown that in vivo drug release can be significantly controlled by the choice of polymers, viscosity grades and polymer loads per patch. Within the range studied drug release can be varied between 10 and 150 min required for a total of 90% of the drug released. More recent studies in this laboratory (Wermerskirchen and Merkle, 1988) indicate that drug release can be sustained for even longer periods of time (> 6 h) at a more or less constant drug release rate. In most cases, however, periods of more than 3–4 h of release are of no practical interest for the buccal patches since it may conflict with common eating intervals. Longer periods

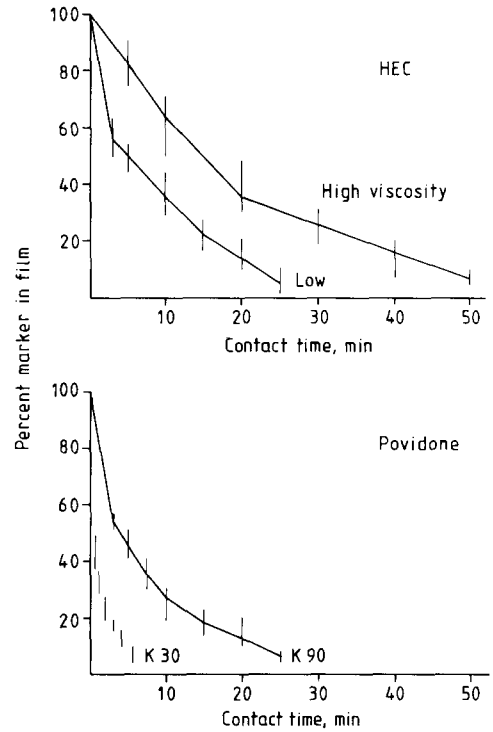


Fig. 5. Effect of viscosity grade of HEC and PVP on buccal release of muco-adhesive patch; all data in same subject; 2.0–2.1 mg polymer per patch; 10 mg sodium salicylate per patch as marker; bars indicate full range of data. HEC: high viscosity Natrosol 250 G, low viscosity 250 L. PVP: high viscosity Kollidon 90, low viscosity Kollidon 30. Backing layer: Multiphor.

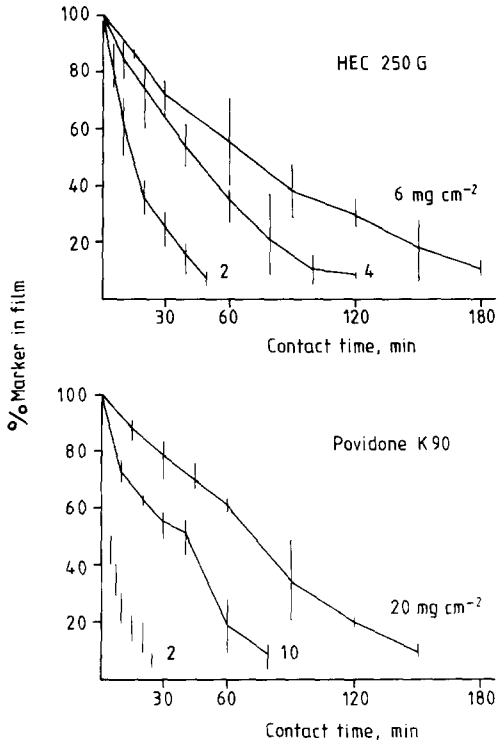


Fig. 6. Effect of polymer load on buccal release of muco-adhesive patch; all data in same subject; 10 mg sodium salicylate per patch as marker; bars indicate full range of data. Backing layer: Multiphor.

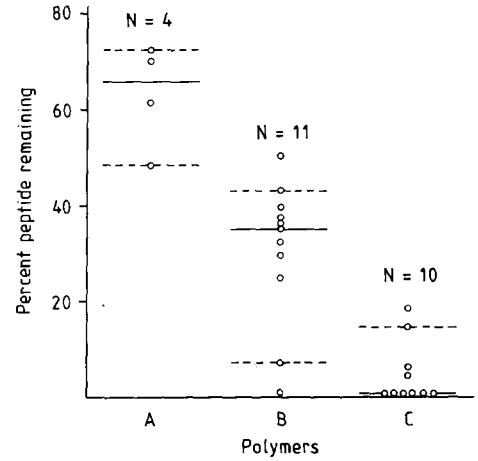


Fig. 7. Release of protirelin from muco-adhesive patches in human subjects after 30 min. A: 19.9 mg protirelin per patch, 6.2 mg·cm$^{-2}$ HEC 250 G. B: 10.4 mg protirelin per patch, 2.2 mg·cm$^{-2}$ HEC 250 G; C: 10.1 mg protirelin per patch, 2.1 mg·cm$^{-2}$ HEC 250 L. Backing layer: Multiphor.

appear to be practical for night-time administration only. Small patches attached to the gingiva at the upper incisors may be designed to adhere considerably longer and may be worn during meals.

*Between-subject variations of in vivo drug release from adhesive patches*

Protirelin release from adhesive patches is also demonstrated in Fig. 7. The data shown are the fraction of protirelin remaining in the patch after a 30 min contact with the buccal mucosa of the human subjects. Three different formulations were evaluated. Both increasing the viscosity grade and the amount of polymer is associated with an increase of the fraction of drug remaining in the patch. The between-subject variability is substantial, but within an expected range, possibly depending on the subjects' habits regarding saliva flow, e.g. talking, jaw and tongue movements, etc. The results also show that by the choice of the polymer the release rates of adhesive patches can be individually tailored to meet the specific needs of a given therapy or drug.

Further information on between-subject variations of drug release is given in Fig. 8. Here the

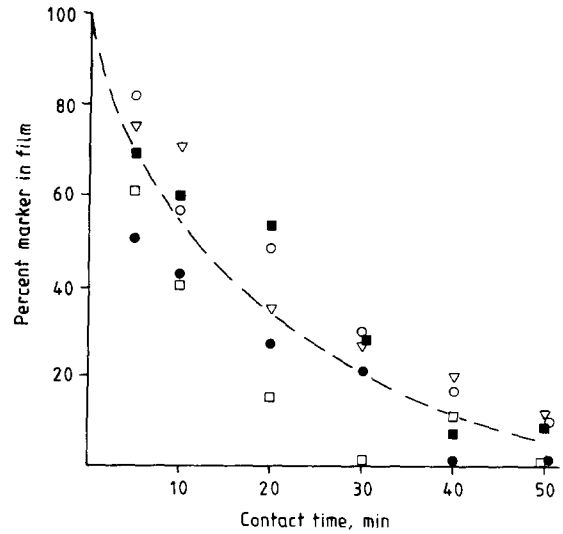


Fig. 8. Release profile of marker (sodium salicylate) from buccal patches in 5 subjects; symbols indicating subjects; marker content of patch was 1 mg·cm$^{-2}$; 2.1 mg·cm$^{-2}$ HEC 250 G. Backing layer: Multiphor.

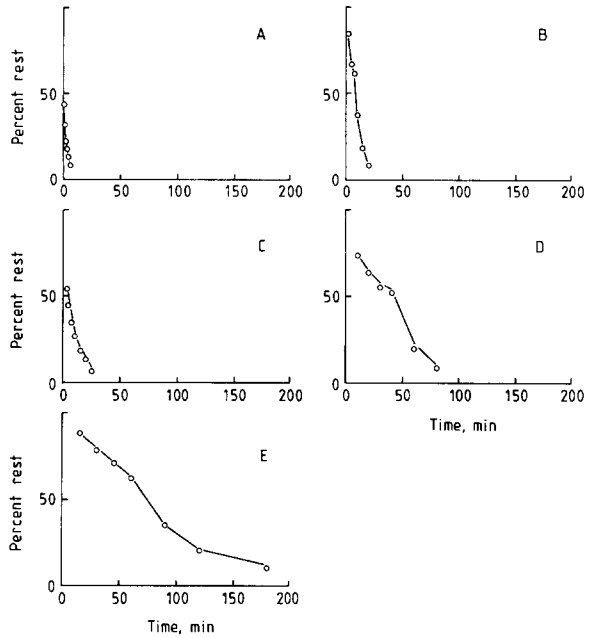


Fig. 9. Correlation of polymer dissolution (lines) and marker release (circles) from PVP 30 and PVP 90 patches; all data in same subject. A: PVP 30, 2.0 mg·cm$^{-2}$. B: PVP 30, 20.5 mg·cm$^{-2}$. C: PVP 90, 2.0 mg·cm$^{-2}$. D: PVP 90, 10.7 mg·cm$^{-2}$; E: PVP 90, 20.5 mg·cm$^{-2}$; 10 mg marker (sodium salicylate) per patch. Backing layer: Multiphor.

release of sodium salicylate as a marker was studied in 5 subjects. Complete release profiles were recorded based on separate release experiments for each of the data points shown in the graph. As before, there is a substantial variability between the subjects, which, however, stays within a reasonable and acceptable range.

*Correlation of polymer dissolution and drug release from patches*

A comparison of polymer dissolution and drug release from PVP 30 and PVP 90 patches using sodium salicylate as a marker is given in Fig. 9. The graphs show the percentage of drug and polymer, respectively, remaining in the patch after given periods of time. The data demonstrate that both processes proceed almost simultaneously, thus indicating a close correlation between drug release and polymer dissolution. It is, therefore, concluded that drug release from such patches is controlled by the dissolution kinetics of the polymeric carrier. Drug diffusion out of the swollen polymeric matrix of the patch appears to play no significant mechanistic role in the overall drug release. This is in agreement with the results of Simonelli (1969) and Merkle (1979) for drug/PVP coprecipitates where the polymer dissolution was the rate-controlling step of drug release. It is assumed that the release from patches made of other water-soluble polymers than PVP 30 and 90 is governed by the same mechanisms.

## Acknowledgements

The authors are grateful to Dr. J. Sandow (Hoechst, AG, Frankfurt) and Dr. G. Weickgenannt (Henning, Berlin) for the RIA and the HPLC analysis of protirelin, respectively. We are also indebted to Hoechst AG and Henning for providing the protirelin used in this study.

## References

Anders, R., Merkle, H.P., Schurr, W. and Ziegler, R., Buccal absorption of protirelin: an effective way to stimulate thyrotropin and prolactin. *J. Pharm. Sci.*, 72 (1983) 1481–1483.

Anders, R., *Selbsthaftende Polymerfilme zur bukkalen Applikation von Peptiden*, (Ph.D. Thesis), Universität Bonn, Bonn, 1984.

Bremecker, K.D., Klein, G., Strempel, H. and Rübesamen-Vokul, A., Formulierung und klinische Erprobung einer neuartigen Schleimhauthaftsalbe. *Arzneim.-Forsch./Drug Res.*, 33 (1983) 591–594.

Bremecker, K.D., Modell zur Bestimmung der Haftdauer von Schleimhauthaftsalben in vitro, *Pharm. Ind.*, 45 (1983) 417–419.

Bremecker, K.D,. Strempel, H. and Klein, G., Novel concept for a mucosal adhesive ointment. *J. Pharm. Sci.*, 73 (1984) 548–552.

Davis, S.S., Daly, P.B., Kennerley, J.W., Frier, M., Hardy, J.G. and Wilson, C.G., Design and evaluation of sustained release formulations for oral and buccal administration. In Bussmann, W.-D., Dries, R.-R., and Wagner, W. (Eds.), *Controlled Release Nitroglycerin in Buccal and Oral Form*, Karger Basle, 1982, pp. 17–25.

Earle, M.P., Experimental use of oral insulin. *Irs. J. Med. Sci.*, 8 (1972) 899–900.

Fraser, H.M. and McNeilly, A.S., Inhibition of thyrotropin-releasing hormone by antibodies. In Griffiths, E.C. and Bennett, G.W. (Eds.), *Thyrotropin-Releasing Hormone*, Raven, New York, 1983, pp. 179–190.

Ishida, M., Machida, Y., Nambu, N. and Nagai, T., New mucosal dosage form of insulin. *Chem. Pharm. Bull.*, 29 (1981) 810–816.

Ishida, M., Nambu, N. and Nagai, T., Mucosal dosage form of lidocaine for toothache using hydroxypropylcellulose and carbopol. *Chem. Pharm. Bull.*, 30 (1982) 980–984.

Ishida, M., Nambu, N. and Nagai, T., Ointment-type oral mucosal dosage form of carbopol containing prednisolone for treatment of aphta. *Chem. Pharm. Bull.*, 31 (1983a) 1010–1014.

Ishida, M., Nambu, N. and Nagai, T., Highly viscous gel ointment containing carbopol for application to the oral mucosa. *Chem. Pharm. Bull.*, 31 (1983b) 4561–4564.

Jarrett, A., The structure of the oral mucosa. In Jarrett, A. (Ed.), *The Physiology and Pathophysiology of the Skin, Vol. 6*, Academic, London, 1980, pp. 1871–1912.

Laczi, F., Mezei, G., Julesz, J. and Laszlo, F.A., Effects of vasopressin analogs (DDAVP, DVDAVP) in the form of sublingual tablets in central diabetes insipidus. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 18 (1980) 63–68.

Levy, G.B., and Fergus, D., Microdetermination of PVP in aqueous solutions and in body fluids. *Anal. Chem.*, 25 (1953) 1408–1410.

Merkle, H.P., Anders, R., Sandow, J. and Schurr, W., Drug delivery of peptides: the buccal route. In: Davis, S.S., Illum, L. and Tomlinson, E. (Eds.), *Delivery Systems for Peptide Drugs, NATO ASI Series, Series A: Life Sciences Vol. 125*, Plenum, New York, 1986, pp. 159–175.

Merkle, H.P., *Untersuchungen an Einbettungen von Arzneistoffen in Polyvinylpyrrolidon*, Habilitationsschrift, Universität Heidelberg, Heidelberg, 1979, pp. 83–148.

Peppas, N.A., and Buri, P.A., Surface, interfacial and molecular aspects of polymer adhesion on soft tissues. In Anderson, J.M. and Kim, S.W. (Eds.), *Advances in Drug Delivery Systems, Controlled Release Series, Vol. 1*, Elsevier, Amsterdam, 1986, pp. 257–275.

Schor, J.M., Davis, S.S., Nigalaye, A. and Bolton, S., Susadrin transmucosal tablets, *Drug Dev. Ind. Pharm.*, 9 (1983) 1359–1377.

Schurr, W., Knoll, B., Ziegler, R., Anders, R. and Merkle, H.P., Comparative study of intravenous, nasal, oral and buccal TRH administration among healthy subjects, *J. Endocr. Invest.*, 8 (1985) 41.

Simonelli, A., Dissolution rates of high energy polyvinylpyrrolidone (PVP)–Sulfathiazole Coprecipitates. *J. Pharm. Sci.*, 58 (1969) 538–549.

Spindel, E. and Wurtmann, R.J., Reversed-phase, ion-pair separation of thyrotropin-releasing hormone and some analogues, *J. Chromatogr.*, 175 (1979) 113–114.

Wermerskirchen, A. and Merkle, H.P., Abstract Nr. 35, 34th Annual Congress of APV, *Acta Pharm. Technol.*, 34 (1988) 11S.

Wespi, H.J. and Rehsteiner, H.P., Erfahrungen mit Syntocinon- und ODA-Buccaltabletten, *Gynaecologia*, 162 (1966) 414–418.