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Comparison of salivary fluoride concentrations after administration of a bioadhesive slow-release tablet and a conventional fluoride tablet

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Abstract—The in-vitro and in-vivo fluoride release of bioadhesive, slow-release tablets prepared from a mixture of polyethylene glycol polymers, containing 0·1 mg of fluoride as NaF was studied, and their ability to sustain fluoride levels in saliva were compared with conventional fluoride tablets with the same fluoride content. In-vitro release experiments showed that the bioadhesive tablets needed 8 h to release all their fluoride compared with < 1 h for the conventional fluoride tablets. In-vivo, the bioadhesive tablets had a retention period of 6 h and could sustain a salivary fluoride level of more than 10 μM above the baseline for 7 h. The conventional fluoride tablets achieved a peak concentration of 0·5 mM directly after dissolution in the mouth, but the fluoride level could not be sustained for longer than 1 h. A good agreement was found between the in-vitro swelling behaviour of the bioadhesive tablets and their in-vitro and in-vivo release characteristics and their in-vivo retention time.

Small concentrations of fluoride, if present in the oral fluids for sufficiently long periods of time, are effective in the prevention of dental caries (Margolis et al 1986). However, topical administration of fluoride in toothpastes, mouthrinses and gels, fails to sustain sufficient fluoride levels over long periods, despite the administration of high doses (Bruun et al 1982).

Recently, we reported sustained fluoride levels in saliva following oral administration of bioadhesive fluoride-containing slow-release tablets (Bottenberg et al 1991). These tablets were able to sustain fluoride levels in saliva for about 6 h with a dose of only 0·1 mg of fluoride.

In this study, another bioadhesive tablet formulation, prepared with a composition of two different mol. wt polyethylene glycol (PEG) polymers, was compared in-vitro and in-vivo with a conventional fluoride tablet. This tablet was either dissolved in the mouth (mixed topical/systemic administration) or swallowed (systemic administration).

Materials and methods

The slow-release tablet (PEG750C) was prepared from a mixture of two different mol. wts of polyethylene glycols (PEG, Polyox, Amerchol, Vilvoorde, Belgium): 95% Polyox WSR-N-750 (mol. wt 300 000 Da) and 5% Polyox Coagulant (mol. wt 5 000 000 Da). The conventional fluoride tablet was prepared using Avicel PH102 (FMC, Philadelphia, PA, USA). Both types of tablets contained 0·1 mg of fluoride as NaF (Merck, Darmstadt, Germany). Before compression the powder was mixed for 5 min (Turbula TA2 mixer, Bachofen AG, Switzerland) and compressed on an eccentric tablet press equipped with flat punches (diam. 7 mm, EKO, Korsch, Frankfurt/Main, Germany). The fluoride content of the tablets was analysed before the dissolution experiments with 6 tablets of each type. The swelling rate of the bioadhesive tablets in water was measured by immersing 6 tablets, each in a preweighed stainless steel basket, in 4 mL of deionized water. The weight of the tablets was determined every hour until no further weight change was observed. The relative weight gain (swollen weight/initial weight) was calculated.

In-vitro fluoride release. The kinetics of fluoride release were determined using a dissolution apparatus as described previously (Bottenberg et al 1991). With bioadhesive tablets, samples of 200 μL were taken every 30 min for 4 h and then every hour until 8 h. The fluoride release from the conventional fluoride tablets was determined using the same technique but as a faster release was expected, samples were taken every 5 min for 30 min and then after 1 h. Fluoride activity was determined with an ion-selective electrode (Orion 96-04, Orion Research, Boston, MA, USA).

In-vivo fluoride release. The experiment was performed essentially as described in our previous paper (Bottenberg et al 1991). Fourteen healthy volunteers, 7 male, 7 female, ranging from 20 to 22 years, participated in this study. Informed consent from the volunteers and permission from the Medical Ethics Committee of the Medical Faculty, Free University of Brussels were obtained. The experimental design included the determination of salivary flow rate before the release experiment, and a low fluoride intake the day before the trial. Every volunteer received one bioadhesive slow-release tablet and one conventional fluoride tablet in separate experiments, performed with an interval of 4 weeks. The conventional fluoride tablet was given to two groups of seven volunteers each. In one group, a purely systemic administration was obtained by swallowing the tablet with 20 mL of deionized water. The other group of volunteers was asked to suck the tablet until complete dissolution in the mouth in order to obtain a mixed topical and systemic administration. The bioadhesive slow-release tablet was applied to the attached gingiva in the region of the upper canine and held there for about 30 s with a slight pressure. Then the tablet and the upper lip were moistened with saliva to prevent sticking of the tablet to the lip. The volunteers were asked to note the retention time of the tablet and remark about the degree of irritation or discomfort.

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Immediately before each experiment an unstimulated mixed saliva sample was taken for the evaluation of the fluoride background. In the case of the bioadhesive slow-release tablets, samples were taken every hour until 8 h after the insertion of the tablet. With the conventional fluoride tablets, an additional sample was taken after the dissolution of the tablet (1 min). Further samples were taken in the conventional tablet groups at 20 and 40 min after the start of the experiment in order to follow the faster release rate of this type of tablet.

Saliva was collected during 5 min in graduated polyethylene tubes (Falcon 2070, Becton-Dickinson, Lincoln Park, USA) and stored at −20°C until analysis, with a maximum delay of two weeks. Salivary fluoride was determined according to the method described by Ekstrand (1977). The fluoride background value was subtracted from the concentrations obtained for the calculation of the area under the curve (AUC) from the individual fluoride concentration/time curves using the trapezoidal rule. The maximal salivary fluoride concentration (C_{max}) and the time of the maximal salivary fluoride concentration (t_{max}) was determined for each volunteer.

For the in-vivo experiment a paired Wilcoxon test was used to test differences between the background fluoride concentration and the fluoride concentrations in the course of the experiment, for each type of treatment..The fluoride concentrations at each sampling time, the AUC, C_{max} and t_{max} between either bioadhesive tablet/conventional tablet (sucked) or bioadhesive tablet/conventional tablet (swallowed) were compared using a Mann-Whitney U-test. A regression analysis was performed to determine whether the stimulated and unstimulated salivary flow rates of the volunteers were related to the tablet retention time and t_{max}.

Results and discussion

The release curves (% of the total release) for the in-vitro experiment are given in Fig. 1. There was a striking difference in release rate between the slow-release and the conventional fluoride tablet. The fluoride release of the conventional fluoride tablets was nearly complete after 30 min and 100% of the fluoride was released after 1 h, whereas the bioadhesive slow-release tablets showed a more gradual release and reached complete release after 8 h. The water absorption of the bioadhesive tablets led to a maximum swollen weight of 3·5 times the initial weight after 6 h. Then gradually the tablets began to disintegrate (Fig. 2.) In contrast, the conventional tablets disintegrated within 1–2 min (data not shown). In-vitro, fluoride release from the bioadhesive tablets was obtained by water uptake from the tablet matrix and diffusion of fluoride through the hydrogel. This could be demonstrated in this study by the good association between the weight gain in the swelling experiment and the kinetics of the fluoride release in-vitro (Figs 1, 2). It is reasonable to assume that the rate of fluoride release is controlled by water uptake in the tablet. This is consistent with theoretical data on the release properties of other controlled-release devices (Harland et al 1988). Diffusion experiments with fluoride through hydrogels showed that fluoride diffusion was not significantly influenced by the presence of hydrogels (Hattab & Lindén 1985).

In-vivo, the bioadhesive tablet formulation was well accepted by the volunteers except for some minor complaints about a

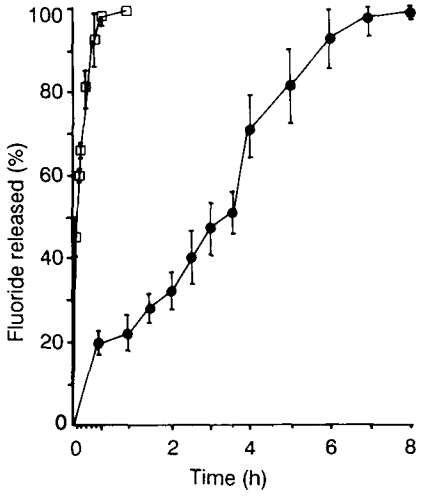

FIG. 1. Amount of fluoride released (% total released) from the conventional fluoride tablet (□, ±s.d., n=4) and the bioadhesive slow release tablet (●, ±s.d., n=4) in-vitro.

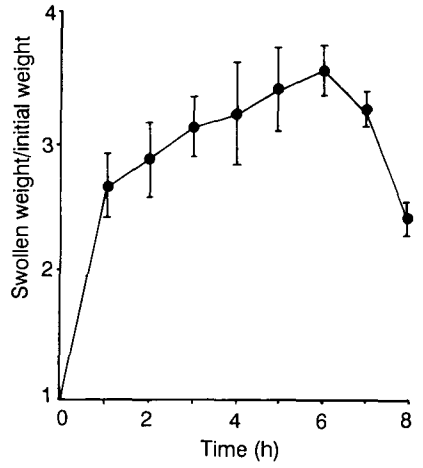

FIG. 2. Mean weight increase ratio (swollen weight/initial weight) of the bioadhesive tablet after immersion in 4 mL of deionized water (±s.d., n=6).

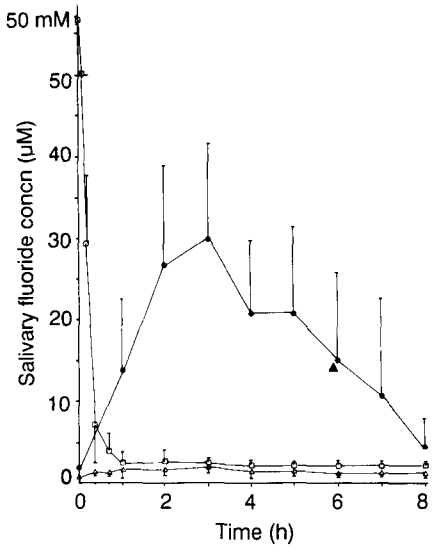

FIG. 3. Mean salivary fluoride concentrations obtained with the bioadhesive slow-release tablet (□, ±s.d., n=14) and the conventional fluoride tablet (sucked ●, ±s.d., n=7; swallowed △, ±s.d., n=7). The arrow indicates the mean retention period of the bioadhesive tablet.

Table 1. In-vivo parameters calculated for different forms of fluoride administration.

Experiment	n	t_{max} (min)	C_{max} (μM L^{-1})	AUC (μM h L^{-1})
Slow-release tablet	14	236±99	35±9·5	62±16
Conventional (sucked)	7	1	463±149·5	10±3
Conventional (swallowed)	7	64±36	1·4±12	1·2±1·3

Mean ± s.d., n = number of volunteers.

feeling of a dry mouth and increased salivary viscosity. This was due to a slow erosion of the tablet surface whereby polymer particles spread in the oral cavity. The bioadhesive tablet remained in place for 6±1 h and no tablet was lost due to detachment. The retention time was not significantly correlated to either unstimulated salivary flow rate (0·8±0·2 mL min^{-1}) or stimulated salivary flow rate (2·0±0·5 mL min^{-1}). However, a good association between the hydration behaviour in-vitro and the retention time in-vivo was found.

The mean calculated t_{max} and C_{max} values are given in Table 1. The salivary fluoride concentration vs time graph in-vivo is shown in Fig. 3. The salivary fluoride concentration obtained with the bioadhesive slow-release tablet was significantly higher than the baseline level during 7 h. As in the in-vitro experiment, the major part of the release occurred within the first 4 h of the experiment but the in-vivo release profiles showed a much higher variance than the in-vitro curve of the bioadhesive tablet. This could be explained by differences in salivary flow which influenced tablet hydration and clearance of solutes in the mouth or by the absorption of fluoride in plaque, saliva or on the oral mucosa (Dawes & Weatherell 1990). A high variance of the AUC values after administration of fluoride in-vivo has already been described by Ekstrand et al (1990).

The conventional tablet yielded a very high C_{max} (Table 1), but the fluoride level in saliva dropped rapidly within 20 min. After 2 h, no significant difference from the baseline level could be found. The swallowed conventional fluoride tablet did not influence the salivary fluoride levels to any significant extent. The AUC value was highest for the bioadhesive tablet followed by the sucked conventional tablet ($P < 0·01$). In the latter case, the major part of the AUC was found within the first 10 min of the experiment.

In this paper, it could be shown that bioadhesive slow-release tablets offer an effective way of sustaining a fluoride level in saliva in-vivo. Other topical fluoridation products such as gels, mouthrinses or toothpastes (Bruun et al 1982), achieve high salivary levels for a short period with doses of fluoride of up to 100 mg per application (Ripa 1990). Also conventional fluoride tablets do not achieve a long-term fluoride administration. If administered systemically, no increase of salivary fluoride could be found with the low dose in this study. Administration of higher amounts (1·0 mg (Oliveby et al 1989)) led to a detectable salivary fluoride increase of about 2·5 μM for about 2 h. However, most of the fluoride present in plasma is taken up in bone minerals, especially in children, and only 1% of the totally administered dose can be found in saliva (Whitford 1990).

When compared with other slow-release devices, those devices described by Mirth et al (1982) had a much longer period of activity but were prepared with a non-hydrating polymer which was not subject to erosion. If a prolonged fluoride administration is desired with bioadhesive tablets, repeated application is necessary. The safety of the bioadhesive tablets is also higher than that of conventional fluoride tablets for which accidents have been reported (Whitford 1990); the swallowing of large numbers of bioadhesive tablets is unlikely because of their adhesiveness. The low dose per tablet and the slow release rate virtually rule out the ingestion of toxic amounts of fluoride. It might be concluded that the application of fluoride-containing, bioadhesive slow-release tablets is a promising way of fluoride application with a high dose-efficiency and safety. Further research is required to evaluate the remineralizing and caries preventive effects of these devices in-vitro and in clinical studies.

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