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Research paper

Salivary fluoride concentrations following applications of bioadhesive tablets and mouthrinses ☆

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Abstract

Presence of elevated fluoride concentration in saliva is important for the prevention of caries. In the present study, we developed an intra-oral bioadhesive tablet aimed at delivering F^- in the mouth over a prolonged period of time. Various tablet formulations were tested in vivo for their tolerance and adhesiveness. Two formulations were selected for further studies on salivary fluoride clearance. For comparison, mouthrinses with increasing F^- concentrations were also examined. Results indicate that a bioadhesive tablet located on the upper gingiva is able to sustain salivary F^- concentrations for about 10 h without major side effects. Mouthrinses with high F^- concentration were able to prolong salivary fluoride retention for more than 6 h.

Keywords: Fluoride; Dental caries; Sustained delivery systems; Adhesion; Salivary fluoride concentrations; Local drug delivery

1. Introduction

Epidemiological studies indicate that dental caries has declined in most industrialized countries over the past 20 years. The improvement of oral hygiene and the widespread use of fluorides have certainly played a key role in the decline of dental caries [1]. It is generally accepted that the preventive effect of fluoride is mainly topical: the continuous presence of low F^- concentrations in the fluid phase surrounding the teeth is now considered essential to have an optimal cariostatic effect [2,3]. Low levels of free fluoride ion have been shown to slow down or even prevent enamel demineralization as well as promote remineralization [4,5].

In this context, it should be noted that daily preparations such as dentifrices and mouthrinses do not provide elevated fluoride concentrations for long periods of time [6–8]. Thus, slow-release systems appear to be of great interest. Such devices were developed in the 1980s [9–13]. They consisted, for the most part, of polymeric devices that had to be placed in the oral cavity by dental professionals and removed when empty. A major advance was made with the development of mucoadhesive tablets to be used for daily application by patients [14,15]. These devices could maintain elevated fluoride concentrations for at least 7 h in vivo.

The aim of the present study was to examine the kinetics of fluoride in the oral cavity using different approaches. The first part consisted in developing an intra-oral bioadhesive tablet intended to deliver F^- over a 12 h period. The rationale is to protect the teeth between the usual twice a day brushing. This approach appears to be more advantageous than daily application with low fluoride containing products. It should also improve patient compliance. In the second part of the study, we tested mouthrinses with increasing fluoride concentration up to 158 mmol/l F^-. The 48 and 158 mmol/l F^- concentrations are clearly higher than those usually found in daily home-use topical fluoride products, and were chosen with the aim of defining to what extent increasing F^- concentrations could lead to a significantly prolonged residence time compared to a commercially available product.

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2. Material and methods

2.1. Subjects

Fourteen healthy volunteers, staff members of the School of Dentistry and the School of Pharmacy at the University of Geneva, 11 women and three men, aged 26–62 years, participated in the trials. All were living in an area with no water fluoridation (F^- concentration <0.010 mmol/l). The oral health status of the subjects was good with no periodontal disease and no active caries. Informed consent was obtained from all volunteers.

2.2. Fluoride formulations

2.2.1. Adhesive tablets

Two different tablet formulations were tested for their tolerance and adhesion time. Both contained 1 mg F^- as NaF as well as Carbopol (BF Goodrich, Cleveland, OH), HPMC (Pro Chem AG, Zürich, Switzerland), and gelatine (Sanofi, L'Isle sur la Sorgue, France) of various grades and proportions (Table 1):

- Type A formulations (100 mg weight, 9 mm diameter, 1.6 mm height) were supplied by Vetoquinol SA (Lure, France). The composition was the same as the product marketed under the name Stomadhex® (Vetoquinol) except that the chlorhexidine originally present was replaced by NaF.
- Type B formulations (50 mg weight, 5 mm diameter, 1.5 mm height) were developed in our laboratory.

2.2.2. Rinses

- Test rinses (5, 48 and 158 mmol/l F^-) were prepared by dissolving NaF (Merck, Darmstadt, Germany) in mouthrinse free of fluoride, specially formulated by Elida Fabergé.
- The rinse Mentadent® C Sensitive (13 mmol/l F^-, Elida Fabergé, Zug, Switzerland) was used for comparison.

2.3. Tolerance and adhesion

Tablets were first evaluated in vivo for their tolerance and residence time in the oral cavity. Good adhesion and tolerance were used as criteria for selecting the formulation to be used for the kinetic study.

Each tablet was tested on two locations in the mouth: one site was mid-line palatal, the other site was vestibular in the upper premolar region. The retention time was determined by checking the presence of the tablet at regular observation times. Tolerance was assessed on an arbitrary scale (1 = very bad, to 6 = excellent) at the end of the test period.

2.4. Saliva collection

On the day of the experiment, each subject was asked to have breakfeast followed by toothbrushing with the non-fluoridated dentifrice before 8 am. The experiment started at 09:00 h with mouthrinses or tablet application. Drinking and eating was not allowed during the first 2 h of the experiment as well as during the 10 min preceding saliva sampling.

Non-stimulated whole saliva was sampled over a 3 min period, during which saliva was allowed to accumulate in the mouth and collected into a plastic container every minute. During the experiment, subjects were asked not to rinse their mouth nor brush their teeth. For experiments lasting more than 12 h, brushing (toothpaste without fluoride) was allowed before bedtime.

Saliva samples were stored at +4°C until analyzed or frozen (−20°C), if analysis was not possible within the week.

2.5. Salivary fluoride clearance

Each formulation was tested twice with at least 1 week wash-out interval. Forty-eight hours before the experiment and during the entire experimental period, subjects were instructed to refrain from food known to be fluoride-rich (mainly fluoridated salt and water, tea, strained poultry, canned, smoked and dried fish) and to use a non-fluoridated toothpaste (Elgydium®, Pierre Fabre Santé, Paris, France).

2.5.1. Bioadhesive tablets

Subjects ($n = 6$) were asked to place the tablet on the upper buccal gingiva by applying mild pressure for 30 s (Fig. 1). After 12 h (10 h for tablets of formulation A), if

Table 1
Composition of the various bioadhesive tablets, all containing 1 mg F^-

Product	A1	A2	B1	B2	B3	B4	B5	B6	B7	B8	B9
Carbopol (type)	20% (971P)	5% (971P)	10% (934P)	10% (934P)	10% (974P)	10% (971P)	10% (974P)	10% (971P)	10% (971P)	10% (971P)	10% (974P)
HPMC (type)	30% K4M	45% K4M	40% K4M	85% K4M	40% K4M	85% K4M	85% K4M	40% K4M	85% K100M	85% K4M	85% K4M
Gélatine	45%	45%	45%		45%			45%			
Lubricant	4%	4%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Drug	NaF (2%)	NaF (2%)	NaF (4%)	NaF (4%)	NaF (4%)	NaF (4%)	NaF (4%)	NaF (4%)	NaF (4%)	CaF_2 (4%)	CaF_2 (4%)

still present, the tablet was removed. Saliva samples were taken at time 0, 15 min, and 1, 2, 3, 4, 6, 8, 10, 12, 22 h.

2.5.2. Rinses

Subjects ($n = 6$) were asked to rinse for 1 min with 10 ml of mouthrinse. Saliva samples were collected at time 0, 5, 15, 30, 45, 60, 90 min, and 2, 3, 4, 5, 6 h after the rinse. In the case of the test formulation containing 158 mmol/l F^-, additional samples were collected after 10, 12, and 24 h.

2.6. Analytical procedure

The day before analysis, the frozen salivary samples were thawed at +4°C. They were homogenized (Vortex®, 30 s) and a 0.5–2 ml aliquot, depending on the volume collected, was placed in a plastic centrifugation tube. After dilution (1:1) with a modified total ionic strength adjustment buffer (TISAB) adjusted to pH 5.5 with 0.2% w/v *trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid monohydrate (CDTA, Fluka Chemika AG, Buchs, Switzerland), the samples were centrifuged at $5000 \times g$ for 30 min and the supernatant analyzed with a fluoride-ion specific electrode (Orion, Model 96-09 combination electrode) connected to a ion-analyzer (Orion, Model 720A, Boston, MA). All reagents were of analytical grade. Samples were analyzed in order of increasing concentration.

2.7. Data analysis

Maximal salivary fluoride concentration (C_{max}) and three time parameters were used for data analysis: the times of salivary fluoride concentrations above baseline values (T_B), above the threshold of 10 μmol/l (T_{10}) and over 50 μmol/l (T_{50}). Previous studies reported that demineralization could be inhibited above these threshold values [5,16,17]. The mean baseline value is an average value obtained from all the individual salivary fluoride concentrations measured at time zero.

In the case of mouthrinses, C_{max} values were extrapolated from the first two points of the salivary profiles according to a linear regression. The threshold of non-baseline levels was set at 5 μmol/l, taking into account inter- and intra-variability as well as variations due to the analytical method. This value has proved to be significantly different from all baseline values recorded during the study ($P < 0.01$).

3. Results and discussion

3.1. Tablet tolerance and adhesion

Results obtained with bioadhesive tablets regarding their in vivo tolerance and adhesion time are reported in Fig. 2. The location of the tablet in the mouth appears to have a great impact on the tolerance and the retention time. Depending on the location, either palatal or gingival, retention times varied from 4–6 h to 7–12 h, respectively.

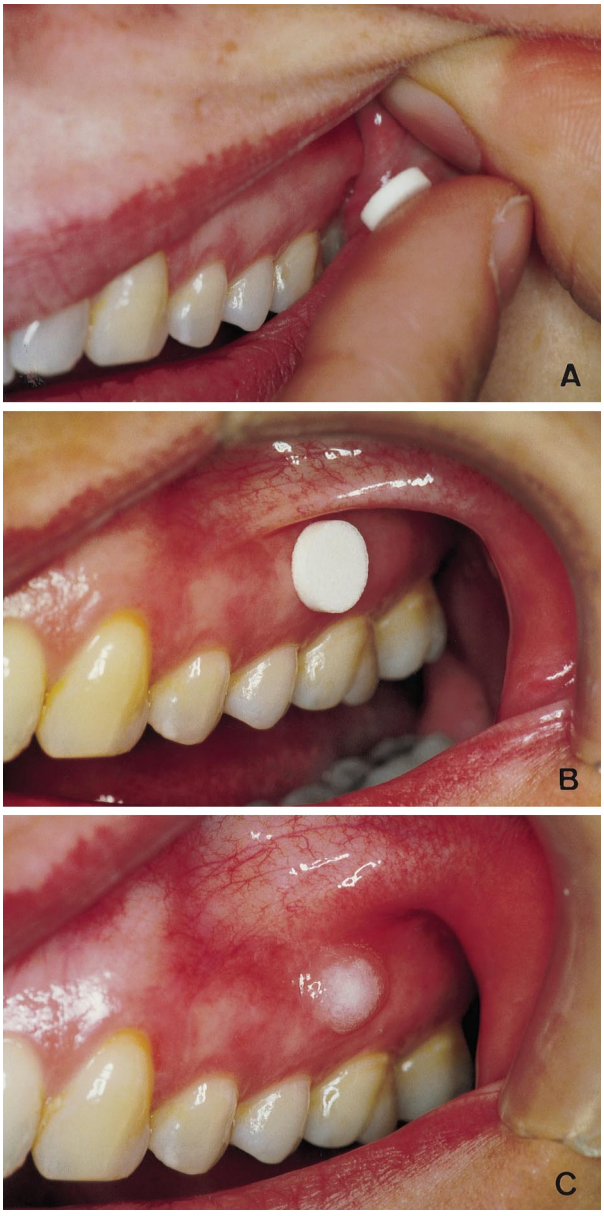

Fig. 1. Intra-oral bioadhesive tablets. (A) Application of the tablet; (B) tablet in situ; (C) hydrated tablet (after 5 h).

Complaints were generally directly related to the duration of adhesion and to the size of the tablet. Palatal mucosa seems to be less sensitive to adhesive polymers than the gingiva, which results in less irritation. However, relatively short retention periods were observed when tablets were placed on the palate, probably because of tongue movements and great exposition to saliva, food and beverages. After 4 h, generally after lunch, the tablet had completely disappeared. Tolerance of type A formulations (large diameter) was much lower than that of type B (small diameter). The main complaints were a burning sensation, discomfort and self-consciousness when speaking or smiling. The formulation of each type which gave the best

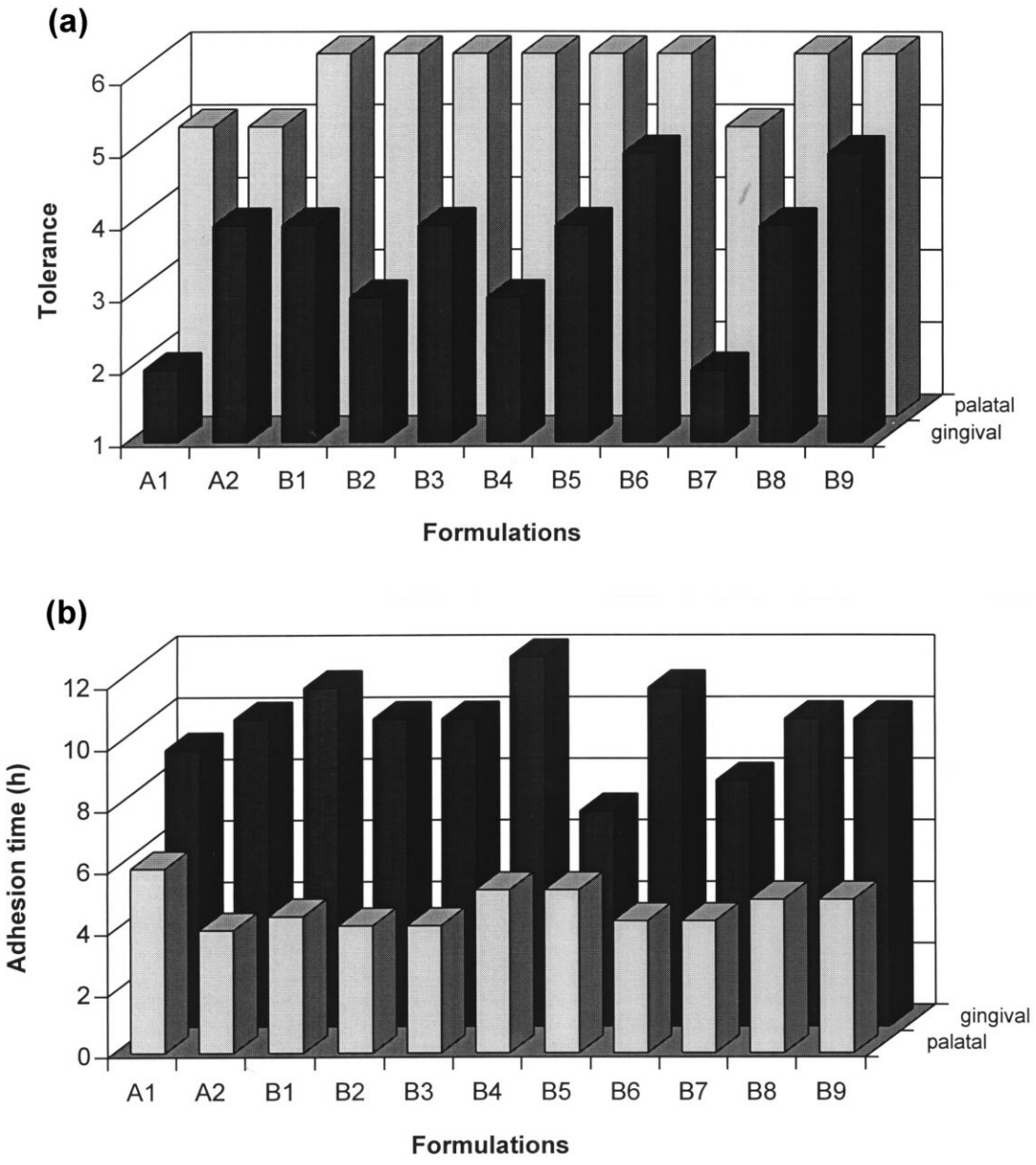

Fig. 2. Tolerance (a) and adhesion time (b) of bioadhesive tablets (for detailed information see Table 1).

results, namely A2 and B6, was retained for the studies on fluoride clearance.

3.2. Salivary fluoride clearance following bioadhesive tablets

For salivary fluoride clearance study, the tablet was placed on the facial aspect of the attached gingiva in the upper premolar region (Fig. 1).

Only three subjects were asked to participate in the clearance study of tablet A because of some discomfort and mucosal irritation with this formulation, versus six for tablet B. Salivary fluoride profiles are presented in Fig. 3. This Fig. shows that elevated fluoride concentrations were maintained over prolonged periods of time with both formulations. A small tablet such as the B6 formulation is particularly desirable as comfort is considerably improved. With such a device, an important aspect from a toxicological point of view, especially in children, is the absence of high concentration peaks as fluoride is slowly released from the tablet.

Based on clinical observations, tablet A2 remained in place for 10 h while retention time for tablet B6 was 9.5 h. Table 2 presents some parameters related to fluoride clearance and concentrations found in the oral cavity. The three time parameters allow the rapid assessment of the duration and the potential efficacy of the fluoride ion after a topical application. In fact, any elevation of the salivary fluoride concentration over baseline values is already bene-

Table 2
Mean C_{max} values and time parameters (±SD) assessing fluoride concentrations and clearance rate in whole saliva after various preparations

Formulations	C_{max} (μmol/l)	T_B[a] (min)	T_{10}[b] (min)	T_{50}[c] (min)
Mouthrinses (mmol/l F^-):				
5 (1 mg F^-/10 ml)	288.8 (178.8)	54.0 (30.0)	35.4 (14.3)	15.3 (5.3)
13 (2.5 mg F^-/10 ml)	939.7 (713.1)	122.2 (75.7)	62.3 (24.8)	23.4 (9.8)
48 (9 mg F^-/10 ml)	3538.4 (1718.0)	241.8 (60.4)	204.5 (53.7)	90.7 (45.3)
158 (30 mg F^-/10 ml)	8143.2 (2890.6)	406.2 (125.0)	266.1 (54.6)	143.4 (49.6)
Adhesive tablets (1 mg F^-)				
A2	307.2 (226.5)	660.0 (54.0)	612.0 (45.0)	276.5 (211.0)
B6	297.7 (119.0)	924.0 (384.0)	672.0 (264.0)	438.0 (138.0)

[a] T_B: time period (min) during which salivary F^- levels were maintained above baseline value (F^- levels ≥5 μmol/l).
[b] T_{10}: time period (min) during which salivary F^- levels were ≥10 μmol/l.
[c] T_{50}: time period (min) during which salivary F^- levels were ≥50 μmol/l.

ficial, even though a significant protective effect only appears above 10 μmol/l F^- and a more extensive inhibition of the demineralization process is probably not achieved below 50 μmol/l F^-, based on in vitro studies [5,16,17]. As for the C_{max} value, it is an interesting indication considering that the higher its value, the longer the salivary fluoride concentrations will stay above the baseline value and therefore have a more prolonged anticaries effect, for a given subject and the same type of formulation. Salivary levels remained above baseline values for 11.0 and 15.4 h, for tablet A2 and B6, respectively. Both tablets maintained fluoride concentrations above 10 μmol/l for more than 10 h. The T_{50} value for tablet A2 was difficult to determine as mean concentrations first fell below 50 μmol/l F^- after 3.6 h, then rose again after 7 h to finally return under this value after about 8 h. Tablet B6 gave a T_{50} of 7.3 h. On average, salivary fluoride levels were maintained over the threshold of 50 μmol/l F^- for 4.7 h.

In a recent study, Bottenberg et al. [18] showed that the location of an adhesive tablet applied daily influences the bioavailability of fluoride at different sites of the oral cavity. It was reported that the center of the palate was a less appropriate site than the lower labial sulcus in terms of fluoride concentrations and area under curve values (AUC) at various sampling sites. It should be noted that previous studies have shown that fluoride concentrations vary from site to site in the oral cavity after mouthrinsing and that clearance was more rapid in the lower anterior sulcus than in the upper anterior labial sulcus [19,20]. It has also been demonstrated that fluoride concentrations occurring around a non-adhesive dissolving tablet in the lower sulcus remained utterly confined to the release site [21,22]. When placed in the upper sulcus, more migration in a mesial direction could be observed. According to these studies, it appears that the upper gingiva position can provide slow clearance and good homogeneity in salivary fluoride profiles, although the best location for an adhesive tablet, in terms of tolerance, retention, distribution and bioavailability, still remains to be determined.

3.3. Salivary fluoride clearance following mouthrinses

Salivary fluoride profiles following different mouthrinses are shown in Fig. 4. The curves obtained for the marketed (13 mmol/l) and 5 mmol/l F^- rinses were consistent with

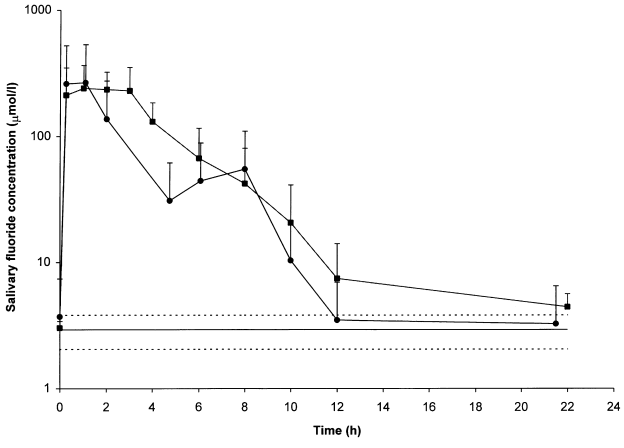

Fig. 3. Mean salivary F^- concentrations following the application of two bioadhesive tablets. ■ formulation B6 ($n = 6$); ● formulation A2 ($n = 3$); —— mean baseline values ± SD (– – –).

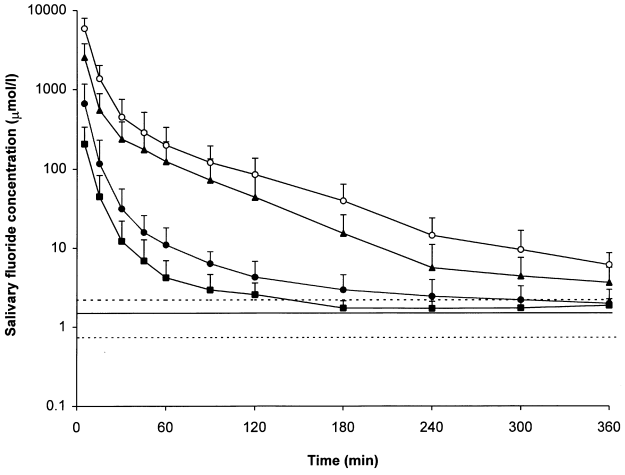

Fig. 4. Mean salivary F^- concentrations after various mouthrinses. ■ 5 mmol/l F^-; ● 13 mmol/l F^- (marketed rinse); ▲ 48 mmol/l F^-; —— mean baseline values ($n = 6$) ± SD (– – –).

the biphasic elimination process reported in the literature [14]. After 2–3 h, F^- levels almost returned to baseline values.

With increasing fluoride concentration in the mouthrinse, we observed higher and more prolonged salivary levels as well as a multiexponential rather than biphasic clearance process. The times during which salivary fluoride concentrations were maintained above baseline were approximately 4 and 6.8 h, for 48 and 158 mmol/l F^- rinse, respectively (Table 2). However, even with such formulations, the supposed optimal protective effect against demineralization (T_{50}) could be achieved for only 1.5 and 2.4 h, for 48 and 158 mmol/l F^- rinse, respectively (Table 2).

Results obtained with mouthrinses are in agreement with previous work on dose–response relationships between salivary fluoride concentration and applied F^- dose [23–26]. However, most of these studies reported equilibrium baseline salivary fluoride levels after regular use of the test products rather than salivary kinetics [23–25]. Moreover, to our knowledge, a 158 mmol/l F^- rinse solution has never been tested. One study reported the use of a 132 mmol/l F^- mouthrinse [27] but only 1 ml was employed for application instead of 10 ml in the present case. In our study, we wanted to know the impact of such highly concentrated mouthrinses on the oral fluoride clearance and therefore on their potential prophylactic effect. Indeed, an increased anticaries efficacy as been reported when increasing the fluoride content of a dental product [23]. We could confirm that increasing dosage resulted in elevated and prolonged oral fluoride levels with an interesting T_B value up to 6 h for the 158 mmol/l F^- solution.

3.4. Salivary fluoride clearance following bioadhesive tablets versus mouthrinses

Compared to the second approach, the sustained-release fluoride tablet is certainly the alternative of choice for young patients. Indeed, with a T_{50} value of more than 7 h, the results are far better than with conventional formulations such as mouthrinses, even if the fluoride content is high. Nevertheless, for adults at risk of dental caries, results obtained with highly concentrated mouthrinses are of interest. The fluoride dose present in 10 ml of a 158 mmol/l F^- rinse (30 mg) is far from the probably toxic dose (PTD) of 5 mg/kg of body weight retained by the WHO [1], and the elevated salivary fluoride levels obtained for more than 6 h are far better than what can be observed following a traditional 13 mmol/l F^- solution. However, generally high fluoride preparations are for professional use and not for daily application by the patients. Thus, we do not know the impact of the daily use of high-fluoride containing products, where CaF_2 is most likely formed, on anticaries effect. Nevertheless, a 48 mmol/l F^- solution, normally aimed at weekly mouthrinsing, has already been used daily during a 4 week period by children aged 11–13 years without adverse effects and giving nearly total caries protection [28]. The authors also observed increased fluoride levels in saliva for 3.5 h to more than 6 h depending on the subject after a single mouthrinse.

4. Conclusion

In the present study, we demonstrated that a F^- containing bioadhesive tablet can maintain elevated fluoride concentrations in saliva for prolonged periods of time. This approach may be of interest in the prophylaxis of dental caries. Designed to be used once a day in patients 'at risk', such a tablet is able to sustain salivary fluoride concentrations for about 10 h without major complaints. Thus, it could offer extra protection in addition to that from the usual home-used topical fluoride products. Our study also showed the importance of F^- concentration in the mouthrinse on salivary clearance. We demonstrated that a high F-containing mouthrinse was able to prolong salivary fluoride retention for more than 6 h. Accordingly, rinses with high F^- content could easily improve the anticaries efficacy between daily treatments. It must be mentioned, however, that such formulations should be restricted to adults, in order to avoid any risk of systemic overdosing.

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