Fluoride Uptake Profiles of Selected European Toothpastes into Hard Tissues and Plaque

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Abstract

- **Objective:** To compare the fluoridating potential of selected European toothpastes using a combination of enamel, dentin, and plaque *in vitro* models.
- **Methods:** Four *in vitro* models were included: 1) Enamel Fluoride (F) Uptake (EFU); 2) Dentin F Uptake (DFU); 3) Enamel Solubility Reduction (ESR); and 4) Plaque F Uptake (PFU). A core set of marketed products was included in all studies, plus a standard toothpaste (1100 ppm F as NaF/silica) and placebo control (the PFU study did not include a placebo control). Test dentifrices: [A] Fluocaril® Bi-Fluoré 250 (1500 ppm F as NaF+1000 ppm F as SMFP); [B] Lacer® Anticaries (2500 ppm F as SMFP); [C] Elmex® Caries Professional™ (1450 ppm F as SMFP+1.5% arginine); [D] Colgate® Triple Action (1450 ppm F as SMFP); [E] Placebo (0 ppm F); and [F] standard toothpaste (1100 ppm as NaF/silica). In all studies (EFU, DFU, ESR, and PFU), assessments were compared for each pair using the Tukey-Kramer HSD test ($p < 0.05$).
- **Results:** In all studies of fluoride uptake, the Fluocaril dentifrice [A] provided the greatest numerical benefit, regardless of the substrate. Statistical groupings were EFU: A > F ≥ B = C ≥ D > E; DFU: A > F ≥ B ≥ C ≥ D ≥ E; PFU: A = B > F = C = D). In demineralization prevention, the Fluocaril dentifrice [A] also provided the greatest benefit (ESR: A ≥ F = C ≥ B ≥ D > E). In all studies that included a placebo control, all of the F-containing dentifrices performed better than the placebo control.
- **Conclusions:** While these results demonstrate that all of the marketed products tested provide effective anticaries benefits, the Fluocaril Bi-Fluoré 250 dentifrice consistently delivered unsurpassed performance. It delivered the highest level of F to plaque, provided greater measures of efficacy in both remineralization and inhibition of demineralization, and delivered substantial improvement in fluoridation of dentin, suggesting the potential for delivering both coronal and root caries benefits.

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Introduction

Fluoride (F) dentifrices are accepted for their ability to help prevent cavities. The widespread use of F-containing dentifrices is generally credited with global reductions in caries over the past several decades.[1-4] Fluoride, delivered from a dentifrice during use, inhibits the process of demineralization and enhances the reversal, or remineralization process through incorporation of an acid-resistant, fluoridated mineral into challenged tooth surfaces.[5,6]

During the early development of F dentifrices, extensive clinical programs were needed to demonstrate the anticaries efficacy of each new formulation. Over the past several decades, significant gains have been made in understanding the processes involved in both inhibiting and reversing carious lesions. This has led to the development of laboratory models capable of predicting the anticaries potential of new products.[7-11] Many of the basic, standardized models, accepted by the United States Food and Drug Administration (US FDA) as suitable for confirming anticaries performance, are used by the dentifrice industry to aid in the development of new products.

In addition to the standardized models, additional models are used by the industry to assess and compare product performance. While some protocols include weeks of repeated treatments under controlled laboratory conditions, others can be completed in a relatively short period of time. Some models incorporate human saliva, others include artificial saliva, and still others rely on aqueous dilution of products in the various test procedures.[12] Depending on availability, bovine or human enamel is used somewhat interchangeably as a test substrate for demonstrating carious lesion inhibition or reversal. A variety of analytical techniques are available to measure the effects of F on treated specimens. Each of these models, many of which have been validated against clinical benchmarks, provides important information about tested products.[13]

Tested products included in the current studies are marketed in various European countries (including France, Spain, Germany, and Poland) and contain 1450 or 2500 ppm F. In Europe, dentifrices containing up to 1500 ppm F are sold as cosmetics or medical devices and are available in the general marketplace, while those formulated at 2500 ppm F have OTC or special DENT status and are sold only in pharmacies. In addition, European dentifrices may contain mixed-active systems rather than the single-active products sold in the United States. Mixed-active products generally include sodium fluoride (NaF) + sodium monofluorophosphate (SMFP), NaF + stannous fluoride (SnF_2), or amine fluoride (AmF) + SnF_2. The product of primary interest in the present evaluation, a mixed-active dentifrice, contains a total of 2500 ppm F, with 1500 ppm F as NaF and 1000 ppm F as SMFP. A previous publication evaluated this dentifrice using one of the available pH cycling models.[14] There is no information in the literature, however, as to how this mixed active dentifrice performs using other routine methods, such as those that are accepted by regulatory agencies as confirmation of anticaries efficacy. In addition, there is no published information available as to how well this product, or any of the products

included in these studies, is able to fluoridate human dentin, a potential indicator of root caries efficacy. Further, no studies have been reported that measured the ability of any of these products to deliver F into plaque, an important element of anticaries mechanism for all fluorides.[15]

The studies reported here include four models that demonstrate the ability of F to release from a dentifrice and react with targeted oral surfaces. Two studies evaluated the ability of the products to enhance remineralization by measuring F incorporated into demineralized enamel and dentin, the third verified the ability of the dentifrices to inhibit demineralization, and the fourth assessed the ability of F to incorporate into plaque. These studies provide perspective on the relative efficiencies of the tested products, and can serve as a basis for dental professionals to recommend products to patients based on their individual needs.

Materials and Methods

All of the studies reported here were conducted following standards for good laboratory practice.

Test Products

A core set of marketed dentifrice products containing 1450 or 2500 ppm F was included in all four studies (Table I). Two of the products contained 1450 ppm F (as SMFP), with one of these also containing 1.5% arginine. The other two dentifrices contained a total of 2500 ppm F; one in which all of the F in the formula was from SMFP, and the other in which the total of 2500 ppm F was comprised of 1500 ppm F as NaF and 1000 ppm F as SMFP. All products were tested within the expiration dates listed on the marketed packages, as determined by the respective dentifrice manufacturers. A standard toothpaste (1100 ppm F as NaF/silica) and placebo control were used in all studies, with the exception of the plaque fluoride uptake study which did not have a placebo control. It should be noted that the hard tissue studies use human teeth, which commonly contain some level of fluoride, so a placebo control is needed. The plaque study uses plaque grown on glass rods, so a placebo control is not necessary.

Table I
Test Dentifrices Included in Each of the Four Studies*

Product Code	Primary Active System	Marketed Name
A	1500 ppm F as NaF + 1000 ppm F as SMFP	Fluocaril® Bi-Fluoré 250
B	2500 ppm F as SMFP	Lacer® Anticaries
C	1450 ppm F as SMFP + 1.5% Arginine	Elmex® Anti-Caries Professional™
D	1450 ppm F as SMFP	Colgate® Triple Action
E	Placebo (0 ppm F added)	———
F	Standard Dentifrice (1100 ppm F as NaF) with silica	Crest® Cavity Protection or USP NaF standard

Fluocaril® Bi-Fluoré 250, Procter & Gamble UK, Weybridge, Surrey KT13 OXP, UK
Lacer® Anticaries, Lacer, S.A. Sardenya, 350 08025 Barcelona, Spain
Elmex® Anti-Caries Professional™, CP-GABA GmbH 20097 Hamburg, Germany
Colgate® Triple Action, Colgate-Palmolive (Poland) Sp. z o.o. Warsaw, Mazowieckie 01-531
Placebo and Crest® Cavity Protection Procter & Gamble Company, Cincinnati, OH, USA

* The ESR study included an additional non-European treatment group for benchmarking purposes. Data for this product had no impact on the conclusions. Statistical evaluations were based on the specific set of products presented in the tables.

Enamel Fluoride Uptake (EFU)

This method, commonly known as FDA Method #40, uses demineralized human enamel specimens as the test substrate.[8] Cores of human enamel were removed from extracted human teeth and prepared per standard procedures.[16] Each specimen was demineralized using 25 ml of a methanehydroxydiphosphonate (MHDP) solution (0.025M lactic acid, $2x10^{-4}$M MHDP at pH 4.5) for 48 hours at 23°C. Following demineralization, specimens were rinsed in deionized water prior to treatment with the centrifuged supernatant of a 1:3 slurry of toothpaste:water (w/w) and then analyzed for F content using the microdrill biopsy technique.[17] In order to ensure analysis of F throughout the full depth of the artificially formed lesions, each specimen was sampled to a depth of 50 µm from the enamel surface. A schematic of the general protocol is included in Figure 1. This procedure was completed in the P&G laboratories.

Dentin Fluoride Uptake (DFU)

The DFU method followed the same general procedure as the EFU protocol (Figure 1), with the exception of using specimens

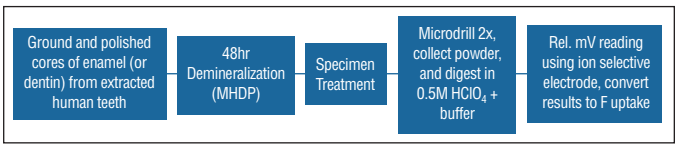

Figure 1. *Schematic of the general protocol for both the EFU and DFU methods.*

prepared from human dentin in place of enamel. Each specimen was demineralized using 25 ml of the MHDP solution (pH 4.5) for 48 hours at 23°C. Following demineralization, specimens were rinsed in deionized water prior to treatment with the centrifuged supernatant of a 1:3 slurry of toothpaste:water (w/w) and then analyzed for F content using the microdrill biopsy technique. Since there was a potential for deeper lesion depth in dentin, compared to enamel, each specimen was sampled to a depth of 200 µm. This procedure was completed in the P&G laboratories.

Enamel Solubility Reduction (ESR)

The ESR method (Figure 2), also known as FDA Method #33, tests the relative ability of oral care products to reduce or inhibit

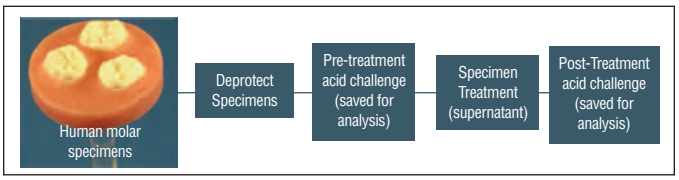

Figure 2. *Schematic of the general protocol used for the ESR method.*

damage to enamel surfaces as a result of challenge by lactic acid.[8] In this model, pre-etched, intact human molars are challenged with 0.1 M lactic acid buffer, treated with the centrifuged supernatant from a 1:3 dilution of toothpaste:water (w/v), rinsed, and then challenged again with the lactic acid buffer in a controlled fashion. The pre- and post-treatment lactic acid solutions are collected and analyzed for phosphorus to determine the level of mineral removed from the tooth during the challenge. This procedure was completed at Therametric Technologies, Inc., Noblesville, IN, USA.

Plaque Fluoride Uptake (PFU)

This method is a variation of the Plaque Growth and Remineralization Model (PGRM) in which artificial plaque is grown on glass rods under controlled conditions in the laboratory. The PGRM method is widely accepted as a means of verifying plaque and gingivitis efficacy of tested formulations.[18,19] In the current study, the level of F deposited and retained in the formed plaque was determined. Plaque biofilm was grown from frozen, pooled human saliva and trypticase soy broth (TSB) at 37°C over three days by dipping abraded glass rods into and out of media in a reciprocating motion (Figure 3). Treatments were made using a 1:5 slurry of dentifrice:water

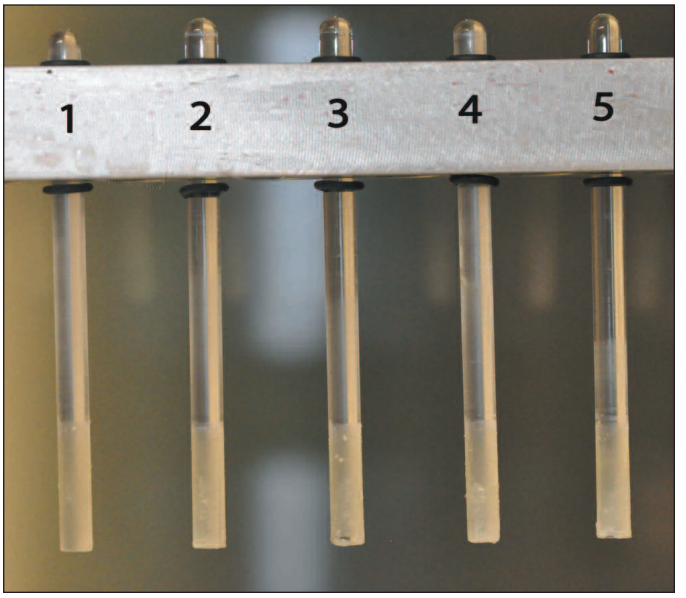

Figure 3. *Image of plaque biofilms grown on glass rods for the PFU study.*

(w/v) for two minutes, then rinsed. After treatment, biofilms were dried, weighed, digested in 1 M perchloric acid, and analyzed for F using a calibrated Ion-Selective Electrode (Model 96-09, Orion). This procedure was completed in P&G laboratories.

Statistical Analyses

In all studies (EFU, DFU, ESR, and PFU), assessments were compared for each treatment pair using the Tukey-Kramer HSD test ($p < 0.05$).

Results

In all four studies, the high fluoride, mixed-active dentifrice [A] provided the greatest level of anticaries performance. Results from the EFU study demonstrated: A > F ≥ B = C ≥ D > E (Table II). In the DFU study, A > F ≥ B ≥ C ≥ D ≥ E (Table III). The ESR results demonstrated A ≥ F = C ≥ B ≥ D > E (Table IV). In the PFU study, A = B > F = C = D (Table V). In the EFU, DFU, and ESR studies, each of the four marketed dentifrices performed better than the placebo control. In the PFU study, all of the marketed products demonstrated significant uptake of F into the plaque biofilm, although a placebo reference was not included in this study.

Discussion

One of the earliest laboratory models for demonstrating anticaries efficacy of F-containing dentifrices (FDA Method #40) was

Table II

Results of Enamel Fluoride Uptake Assessment, Measured as Micrograms of F per Square Centimeter of Surface Sampled (to a depth of 50 µm)

Treatment	F Uptake µg F/cm²	SD	Statistical Grouping*
A	11.50	1.55	a
B	8.24	0.53	b c
C	7.18	0.16	b c
D	6.52	1.07	c
E	4.09	0.79	d
F	8.73	0.83	b

n = 4 specimens per test group
*assessments were compared for each treatment pair using Tukey-Kramer HSD analysis, $p < 0.05$.

Table III

Results of Dentin Fluoride Uptake Assessment, Measured as Micrograms of F per Square Centimeter of Surface Sampled (to a depth of 200 µm)

Treatment	Mean µg F/cm²	SD	Statistical Grouping*
A	40.08	2.96	a
B	31.42	3.51	b c
C	19.13	1.18	c
D	16.38	2.16	c d
E	12.37	1.34	d
F	32.21	2.19	b

n = 4 specimens per test group
*assessments were compared for each treatment pair using Tukey-Kramer HSD analysis, $p < 0.05$.

Table IV

Enamel Solubility Reduction (ESR) Results, Reported as % Reduction

Treatment	origin	pH	Enamel Solubility Reduction [%]	SE*	Statistical Grouping**
A	EU	7.44	23.54	1.67	a
B	EU	8.57	11.22	2.23	b c
C	EU	9.36	17.98	1.33	a b
D	EU	9.62	9.64	1.58	c
E	US	6.96	-3.45	1.80	d
F	US	7.06	16.93	1.33	a b

*SE = Standard Error of Measurement (n = 12)
**assessments were compared for each treatment pair using Tukey-Kramer HSD analysis, $p < 0.05$

Table V

Results of the PFU Study Measuring F Incorporation and Retention in a Plaque Biofilm

Treatment	F Uptake µg F/g Plaque	Statistical Grouping*
A	355.70	a
B	348.42	a
C	188.41	b
D	204.99	b
F	172.50	b

N = 4 treatments rods per test group
*assessments were compared for each treatment pair using Tukey-Kramer analysis, $p < 0.05$.

one in which artificially demineralized enamel was treated with a slurry of toothpaste, and the ability of F to release from the toothpaste and incorporate into the enamel was measured.[8] Although this model may seem simple, its importance cannot be overstated. One of the issues with early toothpaste development was the formulation of products with incompatible ingredients. This resulted in early clinical trials showing that certain F dentifrices, specifically NaF when combined with calcium carbonate abrasives, were ineffective.[20,21] While we now recognize the potential for formulation interactions, this has not completely ensured that all marketed products are free from compatibility issues. In the late 1990s, for example, a product that contained F and "liquid calcium" became available. While certain test models suggested prototypes of the product to be effective,[22,23] other testing, completed on the marketed product using methods designed to assess potential chemical interferences, found that this new product had serious formulation interferences.[24-26] One way to ensure that dentifrices provide high levels of anticaries benefits is to test their performance using multiple models. In that way, it is possible to identify potential formulation outages that an individual model may overlook. The use of four different models in the current evaluation provides the unique opportunity to evaluate these marketed dentifrices from multiple perspectives.

In the ESR model, the mixed-active formula, Fluocaril Bi-Fluoré 250 (Fluocaril 250), provided significantly or directionally greater protection compared to products that contained 1450 or 2500 ppm F as SMFP (Table IV). Results for the three dentifrices formulated with SMFP alone provided some variation in results, with the 1450 ppm F + arginine dentifrice performing directionally better than the 2500 ppm F (SMFP) dentifrice. This result suggests that either the arginine in this formulation, or some other ingredients in the formula, may have had an impact on the overall results in this model. Results of this study suggest that the SMFP/arginine product delivers an enhanced benefit in the ESR model compared to other SMFP-containing products, although all SMFP products had lower ESR percentages than that of the higher fluoride, mixed-active dentifrice in this model.

Both of the hard tissue F uptake models (dentin and enamel) demonstrated statistically significantly better delivery of F for the mixed-active dentifrice compared to the other marketed products (Tables II and III), including one formulated with 2500 ppm F as SMFP. In the EFU model, the 2500 ppm F (SMFP) product performed directionally, although not statistically, better than the 1450 ppm F (SMFP) + arginine dentifrice, which performed equivalent to the 1450 ppm F (SMFP) dentifrice. In the DFU model, the 2500 ppm F (SMFP) product performed directionally better than the 1450 ppm F + arginine product, which performed equivalent to the 1450 ppm F (SMFP) dentifrice. All of the marketed dentifrices performed statistically significantly better than the placebo control, with the exception of the 1450 ppm F as SMFP product, which was directionally better than the placebo. In both of these studies, the mixed fluoride formula resulted in a statistically significant improvement in the ability to deliver F to demineralized tooth surfaces, an important element of the caries prevention mechanism.

Different from the first three models, the PFU method incorporates the use of a plaque biofilm and measures the ability of a dentifrice to deposit F into the biofilm and be retained. The PFU model is a variation of the *in vitro* PGRM. Similar to the results from the other models, the mixed-active formula once again provided the highest level of performance compared to the other test products, although both products formulated with a total of 2500 ppm F were very close numerically, and in the same statistical bracket (Table V). Both of the 2500 ppm F dentifrices performed statistically significantly better than the two that contained 1450 ppm F. Two of the methods in the current evaluation, the ESR Model (FDA Method #33) and the EFU Model (FDA Method #40), are accepted by the US FDA as suitable for confirmation of anticaries efficacy. When using the model in the United States, it is customary to compare performance against one of the USA Pharmacopeia (USP) Reference Standards. The body of evidence within the data presented herein illustrates that Fluocaril 250, a mixed-active dentifrice, delivers significantly greater F uptake into both enamel and dentin, and significantly or directionally greater protection in the ESR testing versus the reference standard (1100 ppm F as NaF/silica) and other marketed dentifrices, including the product formulated with 2500 ppm F (SMFP) alone.

It is recognized that the F uptake studies included in this evaluation did not include salivary dilution of products. However, the same mixed-active dentifrice, Fluocaril 250, and two additional dentifrices that contained 1400 ppm F as AmF, were previously compared in a study that did include salivary dilution of product.[14] In that study, both F uptake and mineralization were measured, using one of the more complex pH cycling models that is used to assess potential anticaries efficacy. Similar to the current body of evidence, the mixed-active dentifrice performed better than any of the other European products included in that study in both measures. The consistency of results across all of these methods provides a convincing argument as to the anticaries effectiveness of this mixed-active dentifrice.

In addition to measuring key parameters regarding enamel caries efficacy in both the current and previous studies, the present evaluation also demonstrated the ability of the mixed-active dentifrice to deliver statistically significantly greater levels of F to dentin, which is important for the control of root caries. Although there are numerous caries clinical trials that have measured the efficacy of F-containing dentifrices against coronal caries, there are only a few that have measured fluoride's effectiveness against root caries. One study by Jensen and Kohout measured the root caries efficacy of an 1100 ppm F (NaF) dentifrice, reporting that the dentifrice provided a 63% reduction in root caries (vs. placebo).[27] In the DFU study conducted here, the mixed-active dentifrice delivered more than twice the level of F uptake into demineralized dentin compared to the 1450 ppm F dentifrices, and almost 28% more than the 2500 ppm F (SMFP) dentifrice. Although other *in vitro* and *in situ* model studies have demonstrated positive root caries effects for SMFP dentifrices,[28,29] there are no well-controlled caries clinical trials that have confirmed root caries efficacy for dentifrices formulated solely with SMFP as the anticaries active. With 1500 ppm F as NaF in the mixed-active formula, the DFU results support the likelihood that this mixed-active dentifrice will provide, in addition to enamel caries benefits, root caries reductions as well.

Incorporation of F into plaque provides a mechanism for extended release of fluoride into the mouth.[30] The levels of fluoride in

such a reservoir are related to the concentration of fluoride in the dentifrice being used.[31,32] As noted by Lynch, *et al*., "… low levels of fluoride, typical of those found after many hours in resting plaque and saliva, and resulting from the regular use of fluoride toothpastes, can have a profound effect on enamel demineralisation and remineralisation."[33] The highest levels of plaque F were delivered from the dentifrices containing the highest levels of F. In a follow-up to a long-term caries clinical trial, Duckworth, *et al.* demonstrated that NaF dentifrices deliver higher levels of F to the plaque than dentifrices formulated with SMFP.[34] In the current study, the dentifrice that delivered the highest level of F to plaque was the 2500 ppm F, mixed-active dentifrice, which was significantly better than the two dentifrices formulated with 1400 ppm F. These results suggest the inclusion of NaF into this dual-active formula has the potential to deliver more effective levels of F to the plaque.

Conclusions

Results from this series of *in vitro* models used to predict anticaries efficacy indicate all of the marketed products tested provide effective anticaries benefits. The Fluocaril Bi-Fluoré 250 dentifrice delivered the highest level of F to plaque, provided significantly greater measures of fluoridation to both enamel and dentin, and the highest level of inhibition of demineralization. The body of evidence gathered for this product suggests the potential for delivering exceptional caries protection, including coronal and root caries benefits.

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