Original Article

Development of a sustained fluoride delivery system

Olga Baturina[a]; Eser Tufekci[b]; Ozge Guney-Altay[c]; Shadeed M. Khan[d]; Gary E. Wnek[e]; Steven J. Lindauer[f]

ABSTRACT

Objective: To develop a novel delivery system by which fluoride incorporated into elastomeric rings, such as those used to ligate orthodontic wires, will be released in a controlled and constant manner.

Materials and Methods: Polyethylene co-vinyl acetate (PEVA) was used as the model elastomer. Samples (N = 3) were prepared by incorporating 0.02 to 0.4 g of sodium fluoride (NaF) into previously prepared PEVA solution. Another group of samples prepared in the same manner were additionally dip-coated in PEVA to create an overcoat. Fluoride release studies were conducted in vitro using an ion selective electrode over a period of 45 days. The amount of fluoride released was compared to the optimal therapeutic dose of 0.7 μg F^-/ring/d.

Results: Only coated samples with the highest fluoride content (group D, 0.4 g of NaF) were able to release fluoride at therapeutic levels. When fluoride release from coated and uncoated samples with the same amount of NaF were compared, it was shown that the dip-coating technique resulted in a fluoride release in a controlled manner while eliminating the initial burst effect.

Conclusions: This novel fluoride delivery matrix provided fluoride release at a therapeutically effective rate and profile. (*Angle Orthod.* 2010;80:1129–1135.)

KEY WORDS: White spot lesions; Fluoride; Decalcification; Controlled release; Elastomeric rings; Demineralization

INTRODUCTION

When oral hygiene is poor, demineralization of the enamel is a concern during orthodontic treatment with fixed appliances.[1–5] White spot lesions (WSLs) or demineralization of the enamel can appear in as few as 2–3 weeks after plaque accumulation adjacent to the orthodontic fixed appliances even when measures are taken to maintain optimum oral hygiene status.[6,7] The formation of these incipient lesions is attributed[6,8] to the prolonged retention of bacterial plaque on the enamel surface around brackets. Enamel decalcifications have been reported[1–5] in as many as 50% of orthodontic patients treated with fixed appliances. Although WSLs may regress, or rarely even disappear, following bracket removal, they often persist and cause esthetic problems.[5] In some severe cases, the occurrence of WSLs during orthodontic treatment may necessitate premature debonding to prevent further damage to the enamel.[9]

In response to the prevalent problem of WSLs, fluoride regimens such as the use of fluoride-containing toothpaste and fluoride mouth rinses have been recommended for patients undergoing orthodontics. Fluoride regimens are reported[4,7,10] to reduce caries during orthodontic treatment with fixed appliances. However, the effectiveness of preventive measures such as administering fluoride by topical application or home rinse programs is limited as a result of the unpredictable compliance associated with these mea-

[a] Research Chemist, Naval Research Laboratories, Alexandria, Va.

[b] Associate Professor, Department of Orthodontics, School of Dentistry, Virginia Commonwealth University, Richmond, Va.

[c] Associate Professor, Research and Teaching Faculty, Department of Chemical and Life Sciences Engineering, Virginia Commonwealth University, Richmond, Va.

[d] Student–Graduate (M.S.), Department of Chemical and Life Sciences Engineering, Virginia Commonwealth University, Richmond, Va.

[e] Professor and Department Chair, Department of Macromolecular Science and Engineering, Case Western University, Cleveland, Ohio.

[f] Professor and Department Chair, Department of Orthodontics, School of Dentistry, Virginia Commonwealth University, Richmond, Va.

Corresponding author: Dr Eser Tufekci, Department of Orthodontics, School of Dentistry, Virginia Commonwealth University, 520 North 12th Street, Richmond, VA 23298 (e-mail: etufekci@vcu.edu)

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sures.[4,7,10] In order to eliminate the need for compliance, manufacturers have incorporated fluoride into the orthodontic adhesives to help prevent or reduce the formation of WSLs. Glass ionomer cements have been shown[11,12] to be effective in releasing the incorporated fluoride to the surroundings in vitro. However, studies[13–16] have shown that the amount of fluoride released is highest on the first day, sharply decreases on the second day, and gradually decreases to undetectable levels by the end of the third day. To provide a long-term low-dose fluoride release, elastomeric ligature ties (rings) impregnated with fluoride were also developed and made available to the orthodontic specialty.[17] Ideally, this method of fluoride delivery would eliminate any need for patient compliance and would ensure replenishment of fluoride source at each orthodontic visit by simply replacing the elastomeric rings. However, results[18–21] on the clinical effectiveness of fluoride-releasing elastomeric rings are somewhat contradictory. Fluoride release from the rings has been found[22] to exhibit an inconsistent profile. Additionally, it has been also reported[22] that fluoride-releasing o-rings have poor mechanical properties in the oral environment, leading to a high incidence of breakage.

Recent advances in biomedical technology provide new approaches for developing controlled delivery systems. Controlled delivery systems allow the release of a therapeutic drug at a rate based on the need of the physiologic environment over a period of time. For this purpose, a wide variety of biocompatible polymers are used as delivery vehicles. Food and Drug Administration–approved polyethylene co-vinyl acetate (PEVA) is very popular because this polymer is highly biocompatible and noninflammatory.[23]

The purpose of this study was to use a novel approach to incorporate fluoride into PEVA, a model elastomere, to provide a controlled release of fluoride ions that would be useful for preventing the development of WSLs in orthodontic patients.

MATERIALS AND METHODS

Preparation of the Samples

There were six experimental groups in this study: group A consisted of PEVA samples that contained 0.50 mL of 1 M sodium fluoride (NaF) solution (aqueous form, equivalent to 0.02 g of NaF powder), group B of samples containing 0.02 g of NaF powder (uncoated), group C of samples containing 0.08 g of NaF powder (uncoated), group C_d of samples containing 0.08 g of NaF powder (dip-coated), group D of samples containing 0.40 g NaF powder (uncoated), and group D_d of samples containing 0.40 g of NaF powder (dip-coated). The control group comprised PEVA samples without NaF.

Initially, 4.2 g of PEVA (40% vinyl acetate, average molecular weight, M_w = 60.4 kDa, glass transition temperature, T_g ca. −36°C; Aldrich Chemical Co, Inc, Milwaukee, Wis) was dissolved in 20 mL of methylene chloride (high-performance liquid chromatography grade; Aldrich Chemical Co). Subsequently, for each group, fluoride-containing PEVA samples were prepared by adding the appropriate amounts of NaF into the previously prepared PEVA/methylene chloride solution.

After the addition of NaF to the previously prepared PEVA/methylene solution, the samples were shaken on a Vortex for 2 minutes followed by a 10-minute treatment in the sonicator to provide a homogeneous distribution of NaF in polymer films. The solution mixture was poured onto a Petri dish and left to bench-dry at room temperature overnight. Once dried, the samples were removed from the Petri dishes and their thicknesses were measured with a micrometer.

Another solution of PEVA/methylene chloride was prepared by dissolving 4.2 g of PEVA in 20 mL of methylene chloride. To prepare samples for the dip-coated groups (C_d, D_d), previously prepared PEVA films were dipped in this PEVA solution. Excess liquid was allowed to drip and the coated films were left to bench-dry overnight. Once dried, the sample thicknesses were measured with a micrometer. The core and the overcoat thickness measurements provided an approximate coating thickness. Figure 1 shows the characteristics of the uncoated (1.31 inches in diameter and 0.03 inches in thickness) and dip-coated (1.31 inches in diameter and 0.39 inches in thickness) PEVA films. Finally, each uncoated and dip-coated film was cut into four pieces, resulting in four samples with a quarter-pie geometry, to test for the homogeneity of each group sample.

Fluoride Release Measurements

A 50-mL buffer solution comprising 45 mL of nanopure water and 5 mL of TISAB III (Thermo Orion, Beverly, Mass) was prepared in a 120-mL plastic container. Prior to measurements, the fluoride ion selective electrode (Corning Glass Works, Medfield, MA, model No. 476135) was calibrated using solutions diluted from 0.1 M NaF standard solution.

Samples (each group, n = 3) were placed individually in plastic beakers containing 50 mL of buffer solution. Fluoride ion release was measured every 5 minutes for the first 2 hours and then daily for 45 days. The measurements were repeated three times. The cumulative release data were plotted for each sample. Data were normalized with respect to the control samples.

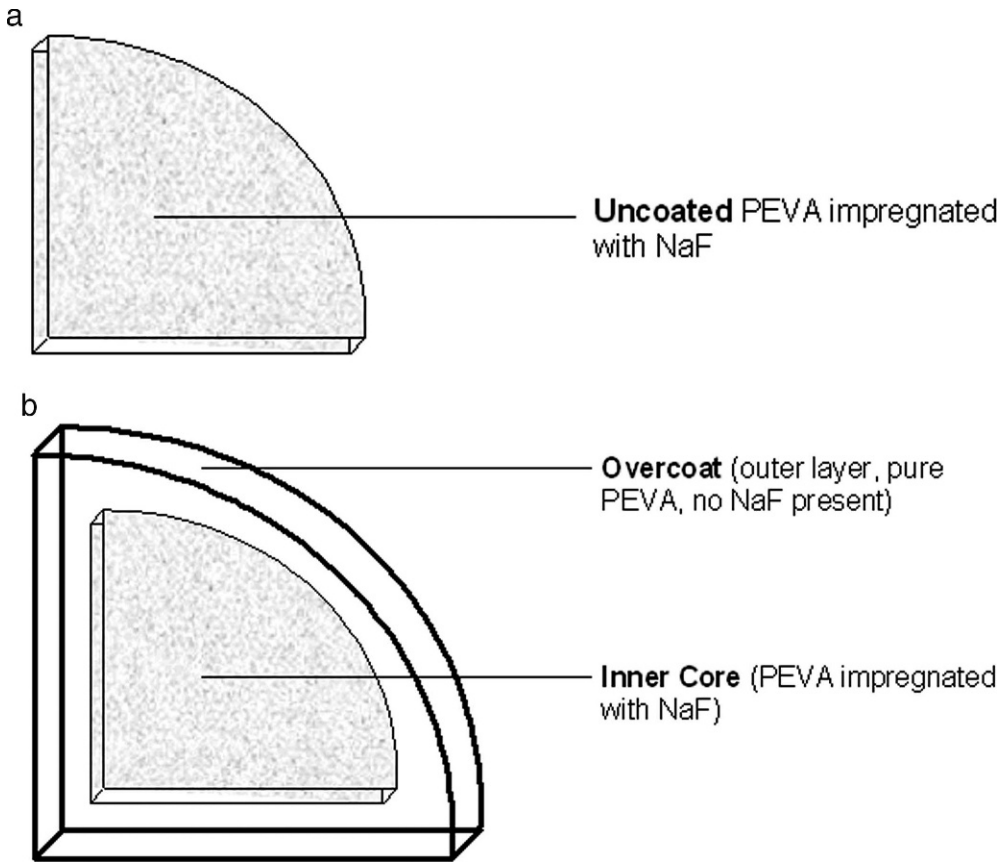

Figure 1. (a) Uncoated and (b) dip-coated fluoride-incorporated PEVA films.

RESULTS

Figure 2 shows the cumulative fluoride release data for group A (0.02 g NaF from aqueous solution) and group B (0.02 g NaF powder) to compare the fluoride release from samples that contained the same amount of NaF (0.02 g) in different forms (aqueous vs powder form). Both groups exhibited an initial burst of fluoride that leveled off after day 1. After the initial burst, fluoride release continued for more than 30 days. Group A samples released 0.16 μg F^-/ring/d and group B samples released 0.06 μg F^-/ring/d; both measurements were negligible compared to the recommended therapeutic rates.[24]

Figure 3 shows the cumulative fluoride release profiles for the uncoated groups with various amounts of NaF in powder form in their structure: group B (0.02 g NaF powder), group C (0.08 g NaF powder), and group D (0.4 g NaF powder). All groups exhibited an initial burst of fluoride that leveled off after day 1. The magnitude of the burst increased with increasing fluoride content, as expected. Following the initial burst, fluoride release continued linearly for more than 30 days, and the average fluoride release was 0.06, 0.31, and 0.88 μg F^-/ring/d, respectively, for groups B, C, and D.

Figure 4 compares fluoride release profiles from the uncoated and dip-coated samples containing 0.08 g NaF (groups C and C_d). Uncoated sample (group C) profiles were characterized by a burst of 17 μg F^-/ring, followed by an average release rate of 0.31 μg F^-/ring/d. The rate of fluoride release became negligible after 25 days. With the dip-coated samples (group C_d), the burst effect was not observed, and the average release rate was 0.41 μg F^-/ring/d over 40 days. However, the release profile for group C_d consisted of three regions. During the first 10 days, the release rate was fast (1.05 μg F^-/ring/d). Between days 10 and 25, a moderate release rate was observed (0.17 μg F^-/ring/d). The rate of fluoride release became negligible after 25 days. This was the case for the uncoated group as well.

Figure 5 compares fluoride release profiles from the uncoated and dip-coated samples containing 0.40 g NaF (groups D and D_d). Group D sample profiles were characterized by a burst of 115 μg F^-/ring followed by an average release rate of 0.88 μg F^-/ring/d. With group D_d samples, the burst effect was not observed. The average release rate was 2.63 μg F^-/ring/d over 40 days. The group D_d profile consisted of two regions. During the first 10 days, the release rate was faster

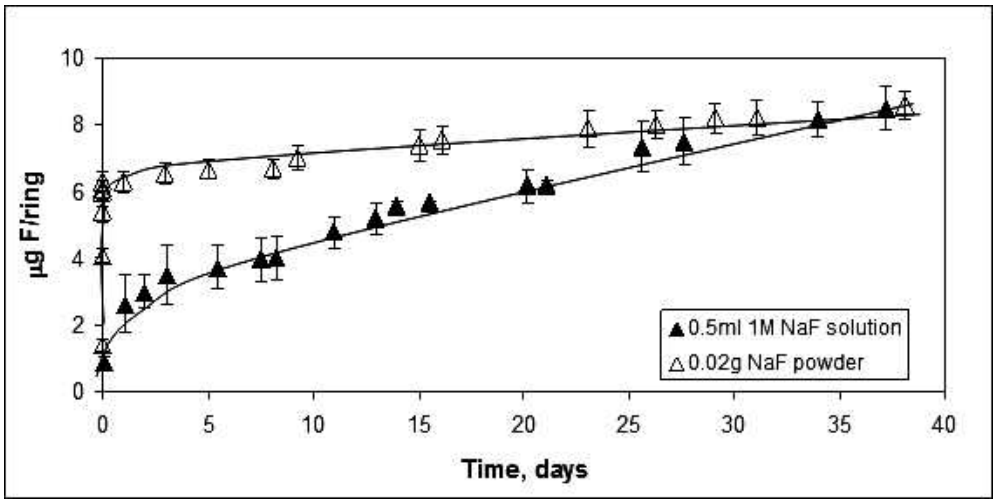

Figure 2. Cumulative fluoride release profiles on uncoated PEVA films containing 0.5 mL of 1 M NaF solution (group A) and 0.02 g of NaF powder (group B).

(6.70 µg F^-/ring/d). After day 10, a constant release rate of 1.43 µg F^-/ring/d was observed. For group D_d, the release rate was still significant even after 40 days.

DISCUSSION

In this study, a novel approach was taken to develop a fluoride delivery system to provide fluoride release in a controlled and continuous manner. It was shown that PEVA samples incorporated with NaF powder coated with a thin layer of pure polymer were able to release fluoride into the surrounding medium in a favorable profile.

The daily recommended supplemental fluoride intake to prevent the demineralization of enamel is 0.024–0.05 ppm.[24] On the other hand, 1 ppm is the toxicity limit, as fluorosis occurs above this concentration. The recommended fluoride concentration range, 0.024–0.05 ppm, corresponds to a fluoride release rate of 1.2–2.8 µg F^-/ring/d, considering the salivary flow[25,26] and assuming 28 elastomeric rings per patient. Therefore, group A, B, C, and C_d samples exhibited fluoride release profiles that were lower than the minimum required therapeutic level, while group D samples met this requirement.

Even though the uncoated group D samples had an average fluoride concentration of 0.88 µg F^-/ring/d, which was higher than the required minimum therapeutic level of 1.2 µg F^-/ring/d, this group was not considered viable as a result of the initial fluoride ion burst of 115 µg F^-/ring, which was higher than the toxicity limit of 51 µg F^-/ring/d (1 ppm), at which point fluorosis becomes a concern. In this study, only dip-coated group D samples were able to release the safe

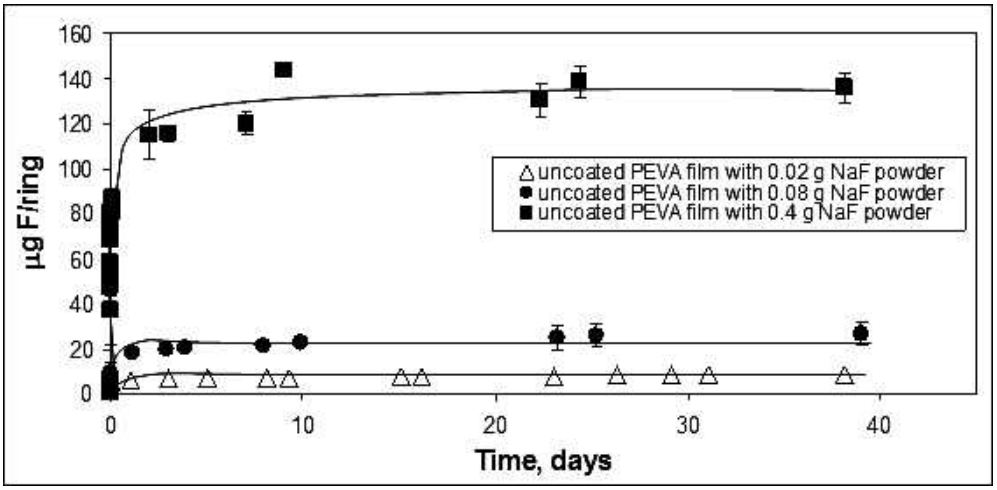

Figure 3. Cumulative fluoride release profiles of uncoated PEVA films containing 0.02 g NaF powder (group B), 0.08 g NaF powder (group C), and 0.4 g NaF powder (group D).

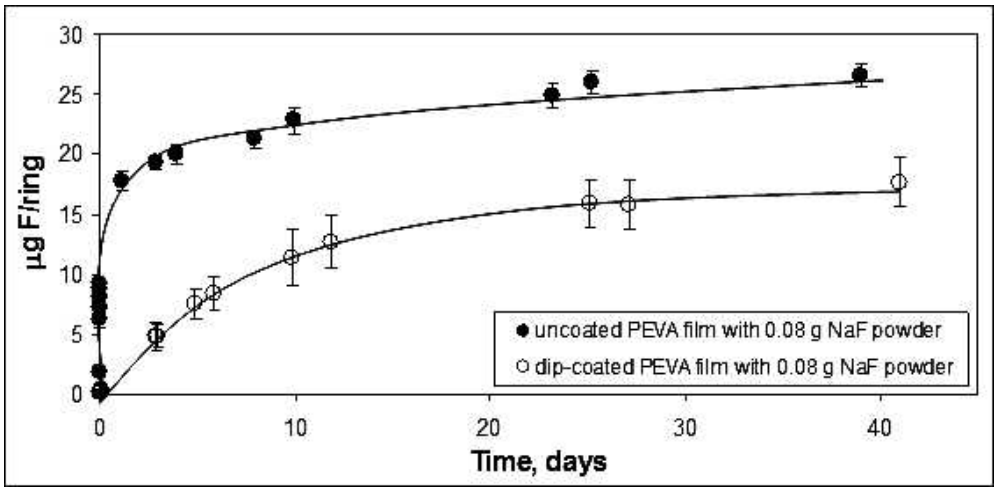

Figure 4. Cumulative fluoride release profiles of dip-coated and uncoated PEVA films containing 0.08 g NaF powder (group C).

therapeutic fluoride concentration. The initial fluoride release was 6.70 µg F^-/ring/d. This rate reached a level of 1.43 µg F^-/ring/d at the end of the 10th day and stayed constant over the course of 40 days.

The diffusion of fluoride through the polymer may be described by Fick's Second Law, a non–steady state diffusion. Since the thickness of the polymer is much smaller than the diameter, radial diffusion was negligible, whereas axial diffusion dominated. Therefore, it is thought that because of this geometry, the overcoat layer becomes a barrier for molecules diffusing in the axial direction. This concept is supported by the finding that the dip-coating technique prevented the initial burst of fluoride from the impregnated polymer films by creating a mass transfer barrier to slow down the diffusion of fluoride from the PEVA film into the surrounding buffer medium. As a result, dip-coated samples exhibited linear fluoride release profiles by eliminating the initial burst effect.

It should be kept in mind that fluoridated community water and fluoride toothpaste are major sources of daily fluoride. In addition, fluoride mouth rinses and supplements have been prescribed for patients at high risk for dental caries.[4] However, these measures have been shown to result in only limited reductions in caries formation, particularly in children, as a result of the lack of compliance as well as the fact that they provide transitory fluoride instead of maintaining a constant fluoride supply. Therefore, the use of fluoridated elastomeric rings in noncompliant patients with poor oral hygiene may be beneficial in preventing the formation of WSLs. Since orthodontic patients are seen every 30 to 45 days for their routine adjustment appointments, it would be ideal to have a continuous fluoride release from orthodontic elastomeric rings between the scheduled appointments. More studies are needed to evaluate the effectiveness of the fluoride-releasing elastomeric rings in preventing WSL formation in vivo.

One of the limitations of this in vitro study is that it may not replicate the complex oral environment. The salivary flow rate, the amount of time required to

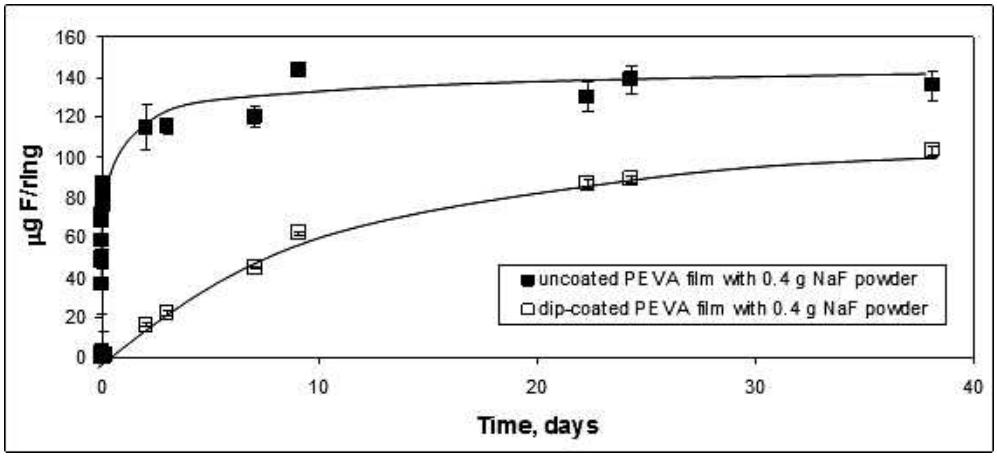

Figure 5. Cumulative fluoride release profiles of dip-coated and uncoated PEVA films containing 0.4 g NaF powder (group D).

replenish saliva, and the composition of the saliva are important factors that could affect the fluoride ion that is readily available around the brackets to prevent demineralization. However, the static immersion test used in the current study is acceptable for the initial evaluation of the fluoride ion release into the storage medium. It is important to keep in mind that the goal of this fluoride-containing polymer is not to provide fluoride for the entire oral cavity but rather to provide a low steady-state release of these ions to inhibit demineralization at the bracket/enamel margins.

The results of this study will be used to design experiments using a continuous-flow cell apparatus along with artificial saliva to mimic more closely the in vivo condition. In these future studies, larger sample sizes will be used, with the ideal fluoride content determined from the current study. This will allow for the in vitro assessment of physiologically relevant variables (salivary flow rate, residual volume, and salivary composition). In addition, the mechanical and physical behavior of fluoride-containing polymers will be investigated, and data will be compared with those of the control group (commercially available nonfluoridated o-rings) to determine which experimental groups exhibit adequate mechanical and physical values required for acceptable clinical performance.

CONCLUSIONS

- In this study, PEVA films with NaF powder incorporated into their structure were able to release fluoride over an extended time period in a consistent manner.
- It was shown that constant fluoride release rates and therapeutic concentrations were attainable by optimizing the fluoride content and overcoat thickness.

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