SPECIFIC AIM

The purpose of this study was to use a novel approach to incorporate fluoride into polyethylene vinyl acetate (PEVA), a model elastomer, to provide a controlled release of fluoride ions that would prevent the development of white spot lesions (WSLs) in orthodontic patients.

STUDIES AND RESULTS

In this study, the first half of the project was dedicated to the preparation of the group samples and the measurement of fluoride release profiles, and the second half was devoted to the collective analysis and interpretation of the data as well as drafting the publications resulting from this study.

During the first six months, various amounts of fluoride were incorporated into PEVA films and fluoride ion release from this non-degradable polymer matrix into a buffer solution was measured for about six weeks. During the final reporting period, a thorough investigation was done to determine the therapeutic and toxicity limits for fluoride for the collective analysis of our data. It was determined that fluoride concentrations 1-to-10 ppm in water defined the range of very mild to severe fluorosis index (see Figure 1)[1]. Accordingly, the toxicity limit was set at 1ppm fluoride in water. Margolis[2] conducted an *in vitro* study which concluded that the minimum fluoride concentration required to prevent demineralization was 0.024 ppm (see Figure 2). Accordingly, during the final reporting period more experiments were run to confirm our initial findings and ensure that the release rates were at therapeutic levels while below the toxic levels.

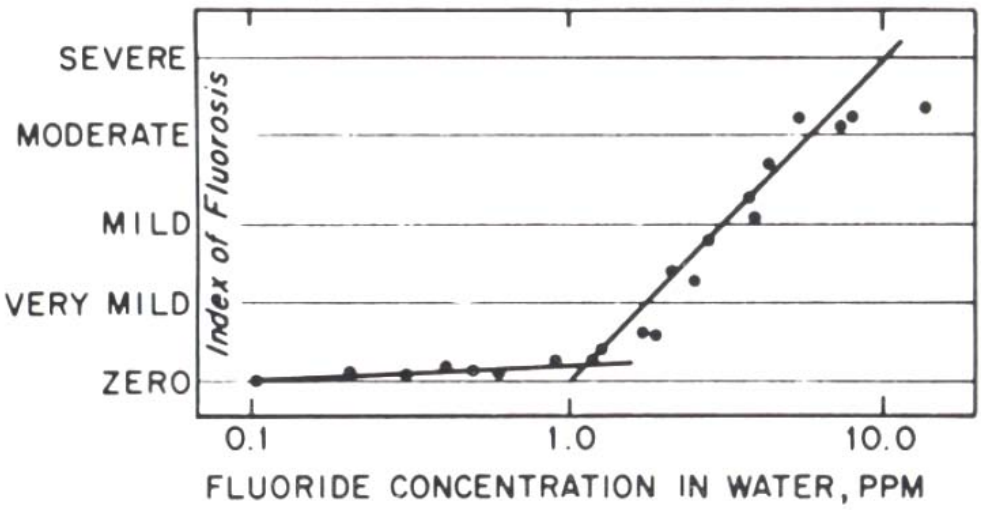

Figure 1. Toxicity (Fluorosis) Limit[1].

The rate of release is determined by the slope of fluoride concentration versus time data that we collect in our labs. Converting the toxicity and therapeutic limits reported in ppm units into μg/ring/day units, which is identical to the units of the slope of ion release data acquired, involves a relatively complicated calculation. These calculations revealed that the toxicity and the therapeutic limits correspond to a slope of 27 and 0.7 μg/ring/day, respectively. In order to achieve fluoride release at the therapeutic level (0.7 μg/ring/day), the fluoride loading and coating thicknesses were recalculated and optimized.

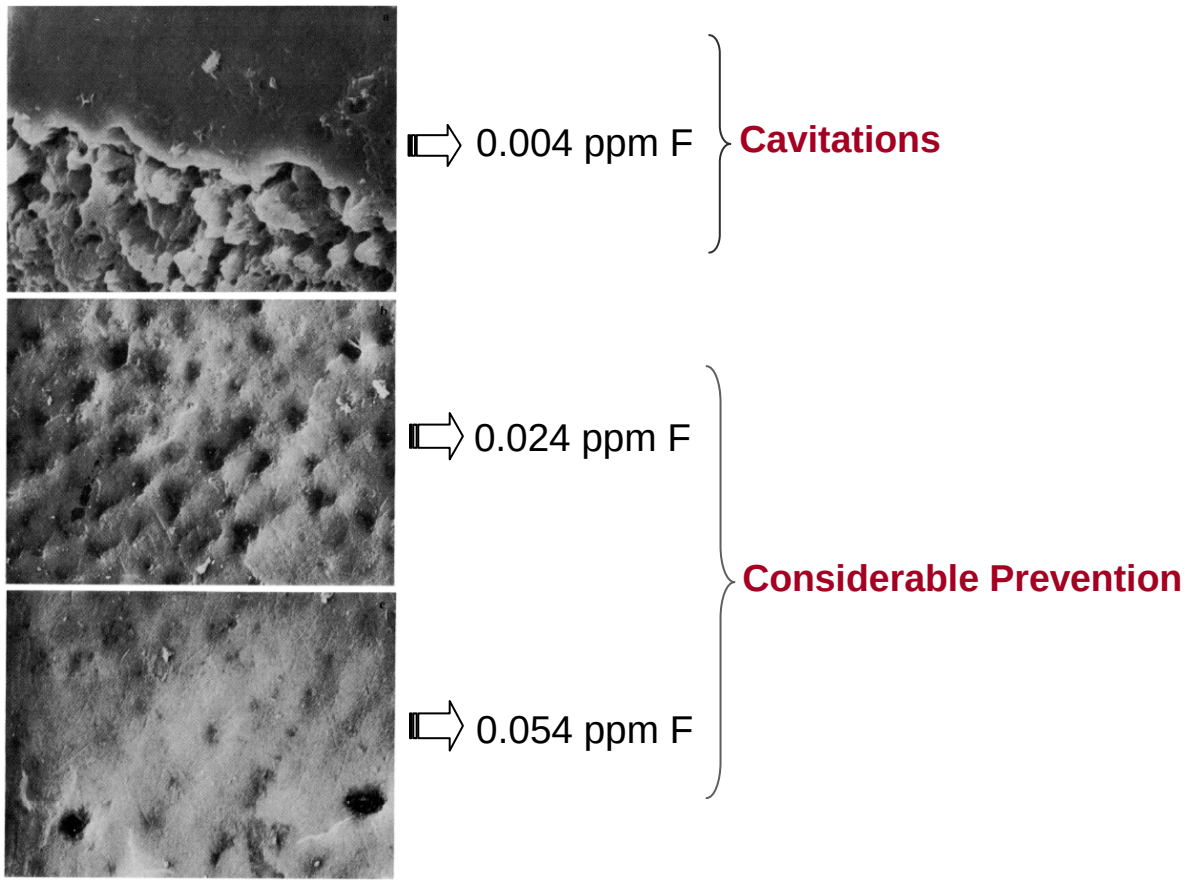

Figure 2. Therapeutic Limit[2].

SUMMARY OF THE PROJECT

Experimental Design:

In this study, the effect of coating thickness, buffer solution temperature, sample geometry and fluoride content on the fluoride release were investigated. The final experimental design is summarized in Figure 3.

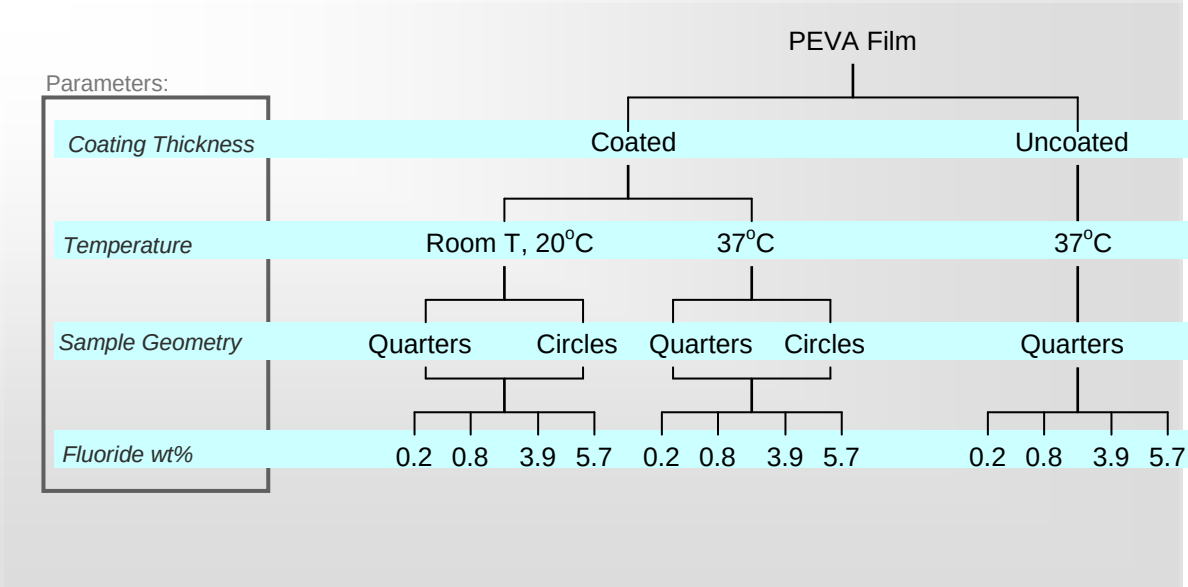

Figure 3. Final experimental design.

Overcoat technique to eliminate the burst effect:

One of the most commonly encountered problems in controlled delivery is the initial burst of the active agent (see Figure 4). In order to eliminate this problem, a mass transfer barrier needs to be created for particularly the active agent that is concentrated at the exterior surface of the product to create a barrier. For this purpose the NaF impregnated PEVA films were dip-coated in a PEVA/THF solution. Once dried, the sample thicknesses were measured with a micrometer. The optimum coating thickness that provided the target performance was determined by fluoride release measurements. Release rates and profiles of the reference samples were compared to the dip-coated samples with the identical fluoride content. It was shown that the burst effect was eliminated with the overcoat. The schematic representation of observed profiles is depicted in Figure 5.

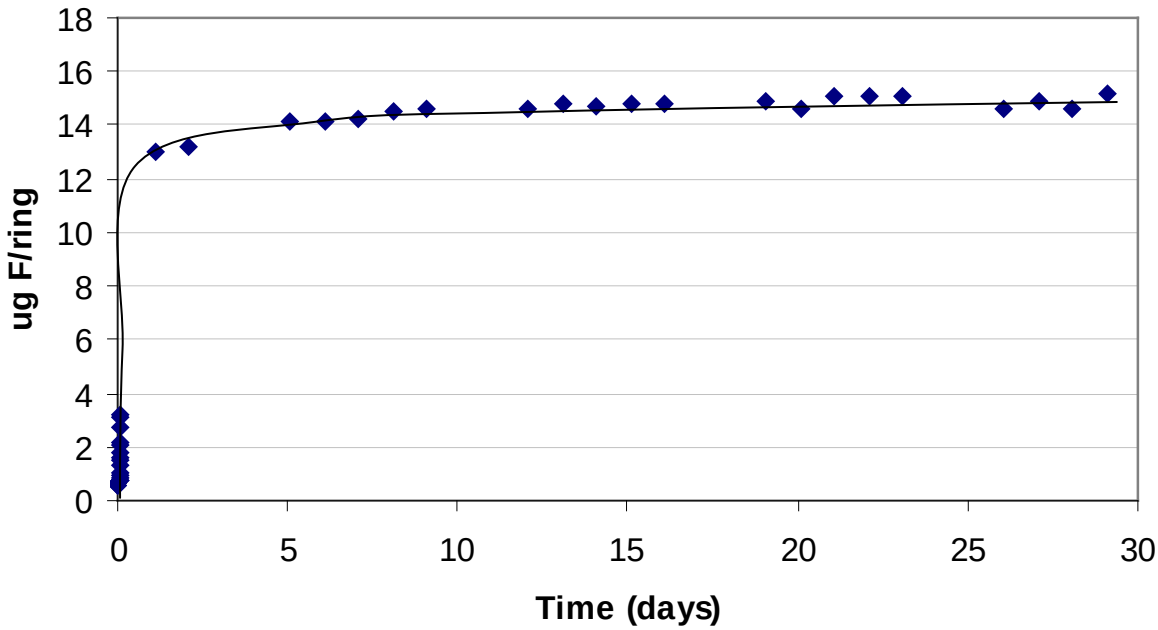

Figure 4. The burst effect: cumulative fluoride release profile for the uncoated samples with a fluoride content of 0.8 wt% at room temperature.

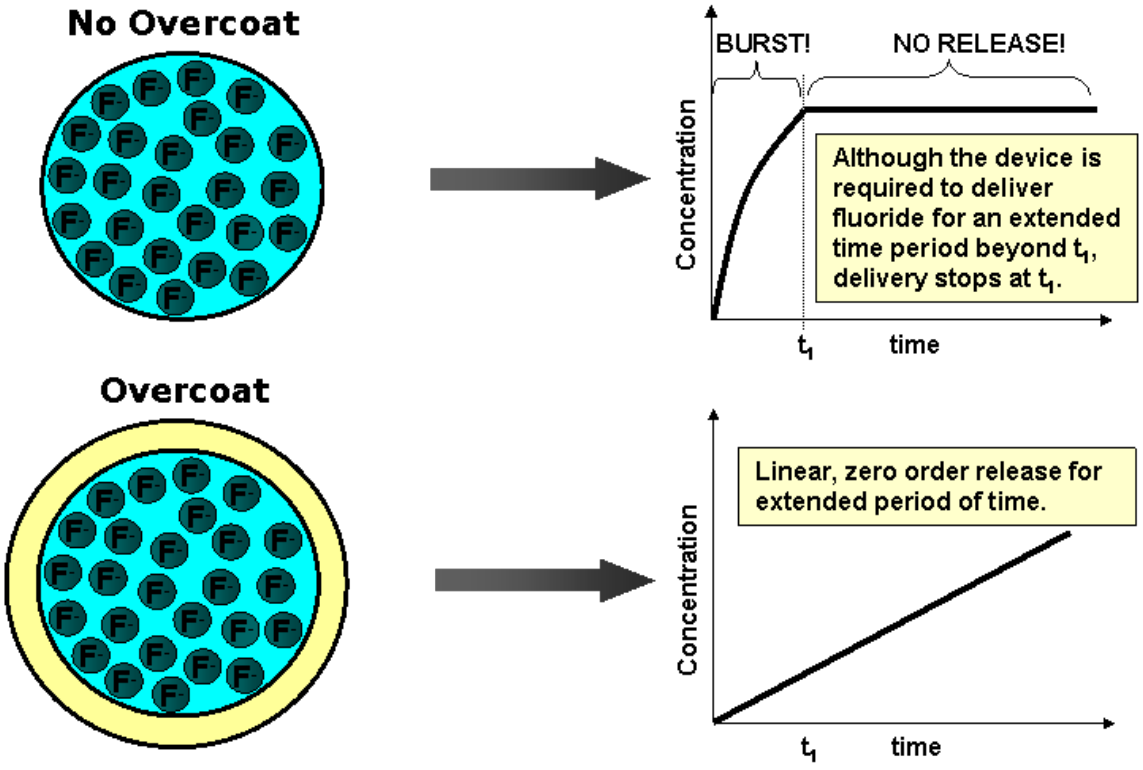

Figure 5. Cumulative fluoride release profiles observed for coated vs. uncoated group samples.

Fluoride content optimization to reach the target release rates:

Previously it has been reported that 0.024 ppm fluoride concentration is the minimum requirement for having a therapeutic effect against caries.[2, 3] Based on this concentration, the required fluoride release rate was calculated. The slope of the concentration vs. time (µg F/ring vs. days) graph indicated a minimum release rate of 0.7 µg F/ring/day to meet the reported requirements for the therapeutic fluoride concentration of 0.024 ppm. Our studies showed that the target rates could be reached by optimizing the fluoride content within the film. A representative data set is shown in Figure 6 where the slope required for the minimum therapeutic concentration of 0.024 ppm (slope > 0.7) is fulfilled by all the experimental groups (Group C samples with 0.8 wt%; Group D samples with 3.9 wt% and Group E with 5.7 wt% fluoride). The 0.1 ppm target slope (slope > 2.7) was fulfilled by Group E samples (5.7 wt% fluoride) only. Well-fit linear trends were obtained for all concentrations tested.

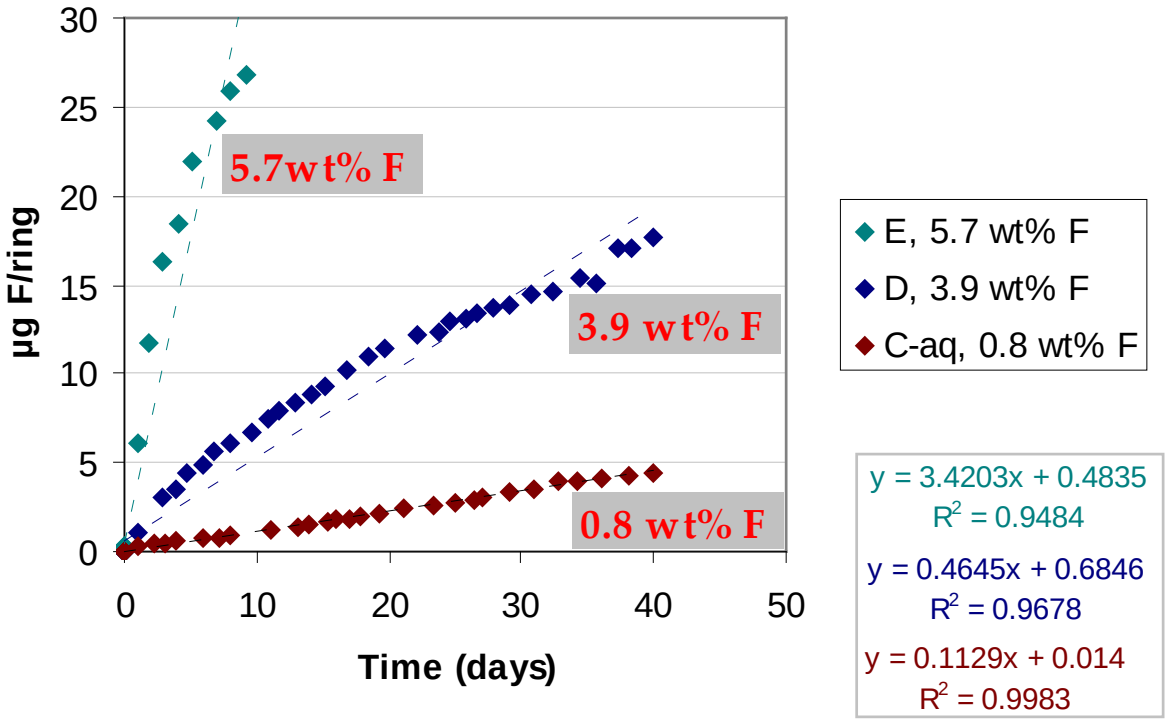

Figure 6. Fluoride release profiles and rates observed for dip-coated group samples with 0.8, 3.9 and 5.7 wt% fluoride at room temperature.

Temperature effect on the release profiles:

Ideally, the buffer solution used in the release studies should be designed to mimic the environment in the oral cavity. Therefore, the ideal buffer environment is artificial saliva at 37°C. However, in our preliminary release studies TISAB buffer kept at a constant temperature of 37°Cwas used. A representative graph is shown in Figure 7. For all fluoride content levels tested, the release studies conducted at 37°C yielded higher release rates. For example, at the lowest concentration level tested, at 37°C fluoride amount release was 0.55 µg F/ring/day as opposed to 0.11 µg F/ring/day at room temperature. In addition, both 3.9 and 5.7 wt% fluoride samples fulfilled the 0.1 ppm target (slope ≥ 2.7) for optimum therapeutic levels of fluoride.[2, 3] These results suggest that higher fluoride release rates may be obtained from samples at in vivo conditions.

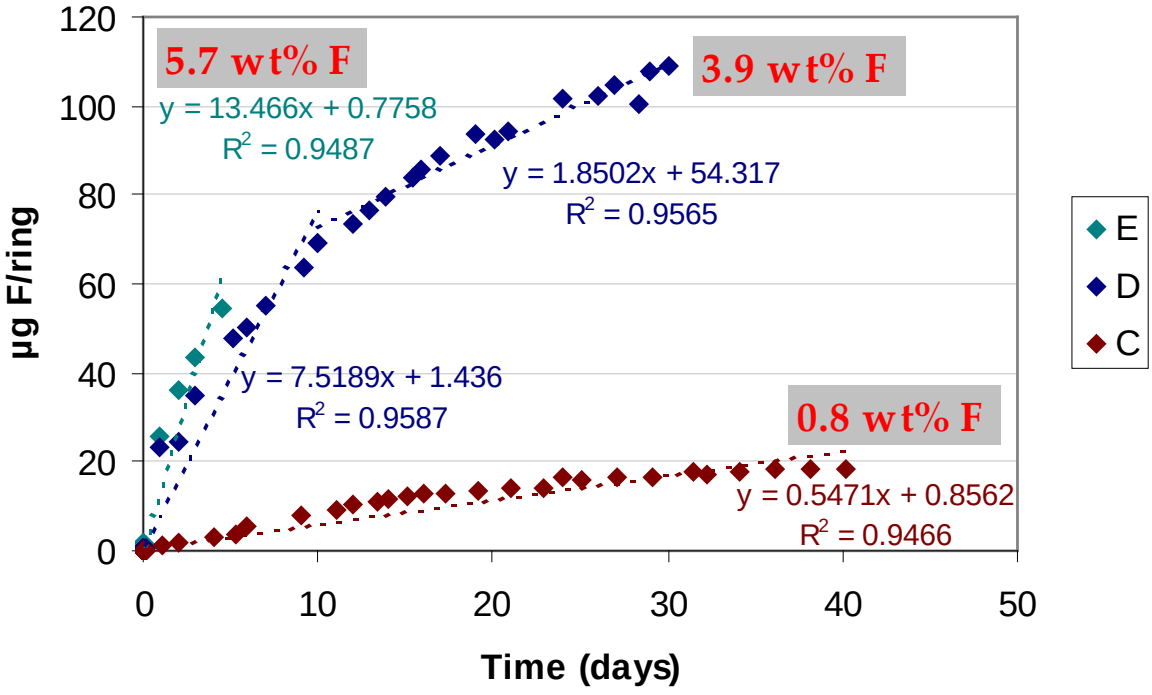

Figure 7. Fluoride release profiles and rates observed for dip-coated group samples with 0.8, 3.9 and 5.7 wt% fluoride at 37°C.

Sample geometry:

Sample geometry did not play an important role in the release profiles. Quarter circles as well as disk shaped samples were tested and similar profiles were observed when all other variables (i.e., coating thickness, fluoride content, and buffer temperature) were kept the same.

A. PROGRESS TO DATE

We have completed a proof of concept and tested the various key parameters. Moreover, we have improved the procedures used in our proposed experimental work. Also, we studied the effect of temperature on the fluoride release rate to better mimic the oral environment. Each experiment was repeated for 3 times. Data was analyzed statistically. All of the data presented here represent the average of three independent experiments. Statistically significant differences between repeat runs were not observed.

Based on our study, a provisional patent application has been submitted. Due to the patent application, the submission of the manuscript was delayed. A list of publications/ presentations can be found in “Section D” of this report.

The data was finalized and a manuscript was prepared for submission to the “Angle Orthodontist’.

REFERENCES

1. E.P. Lazzari, *Dental Biochemistry*, 1976, 164.
2. Margolis, H.C., Moreno, E.C., Murphy, B.J., “Effect of low levels of fluoride in solution ion enamel demineralization in-vitro”, *Journal of Dental Research*, 1986, 65(10), 23-29.
3. Featherstone, J., “Delivery Challenges for Fluoride, Chlorhexidine and Xylitol”, *BMC Oral Health*, 2006, 6 (Suppl I):S8.

C. SUBJECTS

N/A

PRESENTATIONS / PUBLICATIONS

Khan, S., Guney-Altay, O., Tufekci, E., Lindauer, S.J., "Development of Sustained Fluoride Releasing Elastomeric Rings for Orthodontic Applications", *85th Congress of the European Orthodontic Society*, Helsinki, Finland, June 10-14, 2009.

Khan, S., Guney-Altay, O., Tufekci, E., "Development of Sustained Fluoride Releasing Elastomeric Rings for Orthodontic Applications", *AIChE Annual Meeting*, Philadelphia, PA, November 16-21, 2008.

Baturina, O., Tufekci, E., Guney-Altay, O., Khan, S., Wnek, G.E., Lindauer, S.J., "Development of a Sustained Fluoride Releasing System", *The Angle Orthodontist*, to be submitted.

Khan, S., Guney-Altay, O., Tufekci, E., Wynne, K.J., "Synthesis, Characterization and Evaluation of PEVA Elastomeric Rings for Fluoride Delivery against Enamel Decalcification", *Journal of Controlled Release*, to be submitted.

Khan, S., Guney-Altay, O., Kurland, N., Tufekci, E., Wynne, K.J., "Novel Fluoride Delivery Systems: Advanced Dental Materials" *Advanced Drug Delivery Reviews*, to be submitted.