

## Ion Release From Prototype Surface Pre-Reacted Glass Ionomer Sealer and EndoSequence BC Sealer

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### ABSTRACT

**Objective:** Bioactive ions, when incorporated in an endodontic sealer, can contribute to the long-term success of endodontic therapy by combating the re-infection of a tooth and promoting the healing of the periapical bone. The objective of this study was to measure the release of boron, strontium, and silicon ions from surface pre-reacted glass ionomer (S-PRG) filler containing prototype endodontic sealer over a sustained period in comparison to EndoSequence BC sealer in a simulated clinical model using extracted human teeth *in vitro*.

**Methods:** Twelve extracted human anterior teeth were instrumented using ProTaper Next (Dentsply Sirona, Johnson City, TN, USA) files up to size X3 (#30/variable taper) with copious 2.5% NaOCl irrigation. Teeth were obturated using a single-cone technique with a matching size tapered gutta-percha point and one of two endodontic sealers: prototype S-PRG (Shofu Inc., Kyoto, Japan) or EndoSequence BC (Brasseler, Savannah, GA, USA). The teeth were soaked in phosphate-buffered saline (PBS) solution for 336 hours. Periodically, 1-mL samples of the PBS were analyzed via an inductively coupled plasma mass spectrometer to determine the concentrations of ions released by the sealers.

**Results:** The average (S.D.) cumulative release (ng/ml) of boron, silicon, and strontium ions over 2 weeks for the prototype S-PRG sealer was 8614.9 (1264.3), 35758.9 (5986.5), and 3965.2 (145.6), and for EndoSequence BC sealer was 1860.5 (82.7), 164648.7 (16468.1), and 227.7 (4.7). Generalized linear mixed model analysis showed significant differences in ion concentration among boron, silicon, and strontium over time between the two sealer groups (Boron:  $P < 0.0001$ , Silicon:  $P = 0.010$ , Strontium:  $P = 0.028$ ). Of the three ions, strontium had the lowest amount of release for both sealers. The prototype S-PRG sealer showed a rapid initial burst followed by a slow, continuous release of strontium ions.

**Conclusion:** The prototype S-PRG sealer released boron and strontium ions in higher cumulative concentrations over 2 weeks compared to the EndoSequence BC sealer. Both the prototype S-PRG and EndoSequence BC sealers released silicon ions, although significantly more were eluted from the EndoSequence BC sealer. Antimicrobial and osteogenic ion release from sealers is expected to positively influence the post-treatment control of microbial infections to improve periapical healing.

**Keywords:** Boron, endodontic sealer, inductively coupled plasma mass spectrometer, ion release, surface pre-reacted glass ionomer (S-PRG), strontium

Please cite this article as: Bhat A, Cvach N, Mizuno C, Ahn C, Zhu Q, Primus C, Komabayashi T. Ion Release From Prototype Surface Pre-Reacted Glass Ionomer (S-PRG) Sealer and EndoSequence BC Sealer. *Eur Endod J* 2021; 6: 122-7

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Received 11 May 2020,  
Accepted 30 July 2020

Published online: 08 March 2021  
DOI 10.14744/ej.2020.50470

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### INTRODUCTION

The success of endodontic therapy is contingent upon reducing pathogenic micro-organisms in the root canal system by using a careful mechanical process and chemical agents during cleaning and shaping; however, current techniques frequently do not prevent the presence of microbes after treatment (1-3). Failure of root canal treatment is commonly attributed to leakage of the coronal or apical seal or to bacteria that remain in the anatomic irregularities of the canals (4). Accordingly, choosing an appropriate sealer with antimicrobial properties is a strategy to help prevent the re-colonization of bacteria and increase treatment success. EndoSequence BC (Brasseler, Savannah, GA, USA) is a commercially available sealer with antimicrobial attributes (5, 6). This sealer's antimicrobial mechanism consists of a high pH (5, 6), which could reduce bacteria within the canal space and prevent re-colonization. Calcium ions released from the sealer (7-9) with the high pH are known to be the source of bioactivity.

Prototype surface pre-reacted glass ionomer (S-PRG) sealer (Shofu, Kyoto, Japan) has also been used widely used in sealant and resin composites. A S-PRG eluate effectively inhibits the growth and *in vitro* cariogenicity of *S. mutans* (10). Miyaji et al. (11) described the preparation of a surface pre-reacted glass ionomer (S-PRG) filler from a fluoro-boro-alumino-silicate glass having

## HIGHLIGHTS

- Bioactive ions such as boron, strontium, and silicon can contribute to the long-term success of endodontic therapy by combating re-infection of a tooth and promoting the healing of the periapical bone.
- The concentration of ions released from an endodontic sealer may be correlated to that sealer's antibacterial and periapical healing potential.
- Bioactive ion release from EndoSequence BC sealer and prototype S-PRG sealer was measured *in vitro* over a continuous 2 weeks in a simulated clinical model of single-cone root canal filling technique using extracted human teeth.
- Higher concentrations of boron and strontium ions were measured from teeth filled with prototype S-PRG sealer, with a consistent linear release of boron and a rapid initial burst of strontium followed by continuous slow release. The higher concentration of silicon ions was measured in teeth filled with EndoSequence BC sealer.
- This study sets the stage for *in vivo* research to determine the degree to which each sealer can exhibit bioactive properties over time, and whether that leads to the improved success of endodontic therapy.

this composition: 21.6% SiO<sub>2</sub>, 21.6 % Al<sub>2</sub>O<sub>3</sub>, 16.6 % B<sub>2</sub>O<sub>3</sub>, 27.2 % SrO, 2.6 % Na<sub>2</sub>O and 10.4 % F, by weight. The glass powder is surface-treated with polysiloxane and an aqueous treatment of polyacrylic acid. The silicate filler particles undergo an acid-base reaction when the material is mixed with aqueous poly-acrylic acid. The outer surface slightly dissolves, allowing for the gradual release of fluorine, strontium, aluminum, boron, sodium, and silicon ions in water and the recharge of ions from within the glass particles (12-14); the ions are apparent in the composition that is melted. While the fluoride ion primarily assists with remineralization of the enamel (15), the released strontium, boron, and silicon ions are antibacterial and have osteogenic potential (16-18) to improve endodontic outcomes. The prototype S-PRG sealer has shown to exhibit antibacterial and anti-inflammatory effects (11), induce osteogenesis in apical bone (19), and avoid collapse of the dentinal tubule because of its neutral pH (12). Silicon ions are known to promote bone formation and tooth remineralization (20). However, no articles have been published on the amount and speed of ion release from the canal of a root canal filled tooth, which may contribute to the healing of periapical lesions. The comparisons of ion release compared to the EndoSequence BC sealer may elucidate benefits for the use of the prototype S-PRG sealer or the tricalcium silicate sealer.

A inductively coupled plasma mass spectrometer (ICP-MS) was used to measure the number of ions released from the tooth. This technique is commonly used to measure elements in biological fluids and solids, including teeth. One of the advantages of ICP-MS is that it allows multiple elements to be measured at the same time using a very small amount of the

sample. The ICP converts elements into ions which can be then detected by the mass spectrometer (MS).

Thus, the aim of this study was to compare the boron, silicon, and strontium ion release between a prototype S-PRG sealer and an EndoSequence BC sealer in a simulated clinical model using extracted human teeth *in vitro*.

## MATERIALS AND METHODS

### Preparation of teeth

Twelve extracted human teeth were selected. Teeth were included if they were maxillary anterior, single-rooted, and without caries involving the root (IRB#: 121515-014 Not Human Subject Research). The canal was accessed and working length (WL) was determined 1 mm short from the radiographic apex. The canal was cleaned and shaped with the ProTaper Next (Dentsply Sirona, Johnson City, TN, USA) rotary file system up to size X3 by using ProMark torque-limited electric motor (Dentsply Sirona). During preparation, the teeth were irrigated with copious 2.5% sodium hypochlorite (NaOCl); no irrigant was used for smear layer removal.

After instrumentation, the 12 teeth were randomly divided into 2 groups of 6 for single-cone root canal filling with ProTaper Next size X3 gutta-percha cones to match the ProTaper Next file preparation. The canals were dried by ProTaper NEXT size X3 absorbent points (Dentsply Sirona). Each group was filled with either prototype S-PRG or EndoSequence BC (E-BC) sealer, using a single-cone of gutta-percha. Table 1 has a summary of the sealers' composition with working and setting times (14, 21). The S-PRG sealer was mixed; the E-BC sealer was premixed. A consistent volume of sealer (approximately 1 mm<sup>3</sup>) was promptly applied to completely cover the gutta-percha point within the standard working times. The sealer-coated gutta-percha point was inserted to full working length in the canal, cut by Calamus Pack heated instrument system (Dentsply Sirona) at the level of the cemento-enamel junction (CEJ), and condensed. After the setting times (14, 21), the coronal openings were completely sealed with cyanoacrylate adhesive before *in vitro* soaking.

### *In vitro* soaking of teeth

The root canal filled teeth were soaked in sealed 1.5-mL polyethylene tubes (VWR, Radnor, PA, USA) filled with 1 mL of phosphate-buffered saline (PBS) (VWR, Radnor, PA) solution for 2 weeks (336 hours). Teeth were stored in a 37°C incubator to mimic the conditions of the oral environment. Samples (1-mL) were taken at 3, 6, 12, 24, 48, 120, 168, and 336 hours using a manual pipette. Samples were obtained after first agitating the solution. One mL of fresh PBS solution was replaced post-sampling, and samples were stored in the incubator between sampling intervals.

### ICP protocol

Boron (B), silicon (Si), and strontium (Sr) ion release was measured with an Inductively Coupled Plasma mass spectrometer (ICP-MS) (Agilent 7500 with Autosampler ASX-500, Santa Clara, CA, USA). The ICP-MS detected the absorbance wavelengths of the ions in the collected PBS. High-purity nitric acid (Lot #NX0407, EMD; Millipore, Billerica, MA, USA) and MilliQ water

**TABLE 1.** Summary of endodontic sealers' composition, working, and setting times

Type	Product name (Company, country)	Composition <sup>11, 30)</sup>	Lot # time	Working time	Setting time
Glass ionomer	Prototype S-PRG glass ionomer	Powder Zinc oxide-based inorganic compound filler, Surface reaction-type pre-reacted glass ionomer (S-PRG) filler, Unknown additives	#051401	N/A	13 minutes <sup>14)</sup>
	(Shofu, Kyoto, Japan)	Liquid Polycarboxylic acid-derived, Water, Unknown additives			
Tricalcium silicate	EndoSequence BC  (Brasseler, Savannah, GA, USA)	One paste Zirconium oxide, Calcium silicates, Calcium phosphate, Calcium hydroxide, Thickening agents, Unknown liquid	#(10)16002SP	>24 hours <sup>21)</sup>	2.7 hours <sup>21)</sup>

were used to prepare a 2% nitric acid solution for sample and standard preparations. A standard mixture containing Si (50 µg/mL), Sr, Na, B, and Ca (each at 100 µg/mL) was used (Lot #89800-568; BDH Chemicals, Darmstadt, Germany). The standard mixture was diluted 20-fold with 2% nitric acid to 1/1000, such that the solution contained 50 ng/mL of Si and 100 ng/mL each of Sr, Na, B, and Ca ions. The internal standard was lutetium (10000 µg/mL) (Lot #R01254; Ultra Scientific, North Kingstown, RI, USA).

Standards and samples were spiked with the internal standard of lutetium at a concentration of 100 ng/mL. Phosphate-buffered saline (PBS) was diluted 20-fold with 2% nitric acid for use as a matrix blank. Matrix blanks, standard solutions, and samples were assayed in duplicate or triplicate. Counts per second (CPS) for each analyte of interest in the matrix blank were subtracted from the standard and sample results for corresponding analytes. The absorbance wavelength was measured in ng/mL for each of the samples. All samples were measured in ng/mL within the PBS solution.

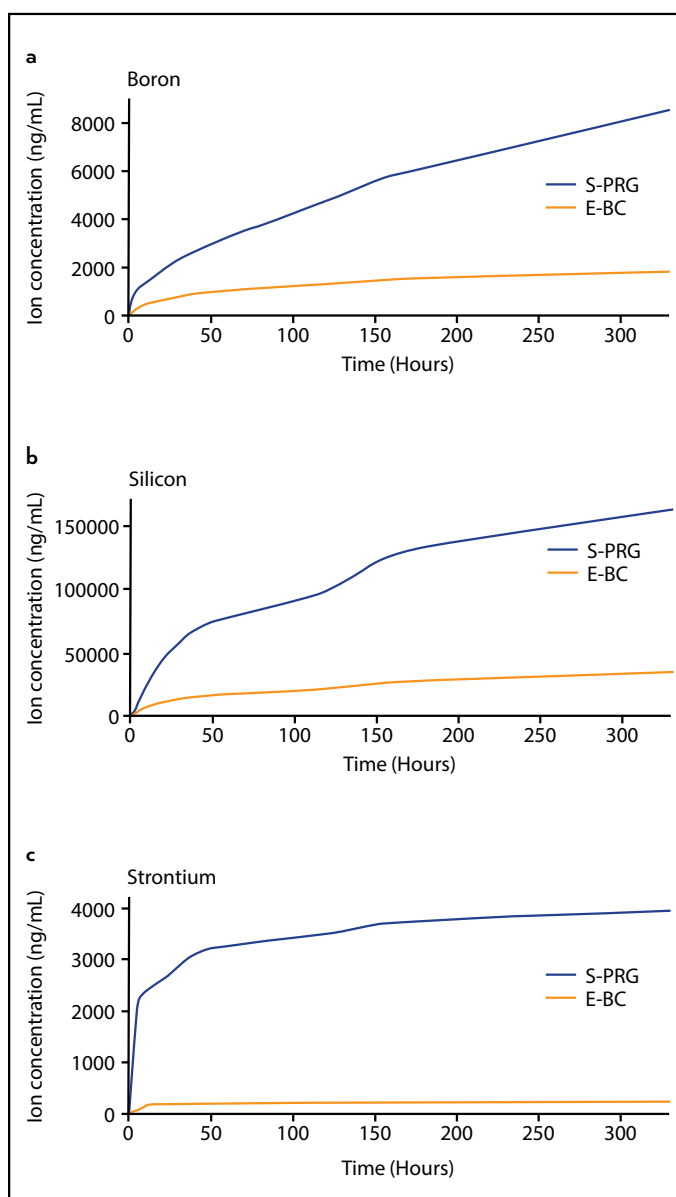
### Statistical analysis of data

Two-sample t tests were used to determine if there were significant differences in ion release of boron, silicon, and strontium between the two sealer groups. Generalized linear mixed models (GLMMs) were used to detect significant differences in ion release over time between the two groups. All analyses were performed with the SAS/STAT 15.1 statistical package (SAS Institute, Cary, NC, USA).

### RESULTS

Table 2 shows the average cumulative concentrations of boron (B), silicon (Si), and strontium (Sr) ion release over 336 hours. Figure 1 shows the cumulative ion release over time for the two sealers.

The silicon ion release was the highest among the three ions. The average cumulative silicon ion release by the S-PRG sealer was significantly lower than that released by E-BC sealer ( $P < 0.05$ ) (Table 2 and Fig. 1b). The average cumulative silicon ion releases by the S-PRG sealer and E-BC sealer were 35800 (6000) and 165000 (16500) ng/ml. The speed of boron and silicon ion release from both sealers was constant (Fig. 1a, 1b).



**Figure 1.** Comparison of average cumulative ion releases of (a) boron, (b) silicon, and (c) strontium over time in the prototype S-PRG sealer (S-PRG) and EndoSequence BC sealer (E-BC)

**TABLE 2.** Average cumulative ion release over 336 hours

Ion	Hours	Prototype S-PRG sealer (S-PRG)		EndoSequence BC sealer (E-BC)	
		Average cumulative [ng/ml]	Standard deviation (SD)	Average cumulative [ng/ml]	Standard deviation (SD)
Boron	3	806.7	788.5	201.1	41.3
	6	1110.2	220.9	332.8	28.5
	12	1440.1	187.9	497.4	41.0
	24	2016.5	418.2	707.5	62.4
	48	2919.3	733.6	970.3	75.7
	120	4713.8	1187.3	1322.5	96.6
	168	5905.7	566.8	1543.5	62.1
	336	8614.9	1264.3	1860.5	82.7
Silicon	3	2490.7	3369.5	5734.6	4146.1
	6	5719.4	4478.8	15687.4	7412.2
	12	9152.5	4600.4	31160.3	10947.8
	24	12848.4	4742.2	51119.9	13495.5
	48	17035.1	5022.0	73788.5	15403.9
	120	22187.4	5241.2	98948.8	16739.4
	168	27746.2	5524.1	130297.8	14776.5
	336	35758.9	5986.5	164648.7	16468.1
Strontium	3	1237.8	1650.3	27.0	18.4
	6	2168.5	1432.7	59.9	35.3
	12	2421.1	232.4	155.7	6.0
	24	2694.0	294.1	172.6	6.4
	48	3200.6	656.7	187.5	7.5
	120	3500.0	234.7	201.4	6.1
	168	3742.3	212.1	214.7	5.5
	336	3965.2	145.6	227.7	4.7

The S-PRG sealer released a significantly higher ( $P<0.05$ ) number of boron ions than the E-BC sealer (Table 2). The cumulative boron ion releases by the S-PRG sealer and E-BC sealer were 8600 (1260) and 1860 (83) ng/ml.

Fewer strontium ions were released than B or Si from either sealer. The Sr released by the S-PRG sealer was significantly higher ( $P<0.05$ ) than that released by the E-BC sealer (Table 2 and Fig. 1c). The average cumulative strontium ion release by the S-PRG sealer and E-BC sealer were 3.970 (146) and 228 (5) ng/ml. The strontium ion release had a rapid initial burst followed by slow continuous release from the S-PRG sealer. The Sr ion release was slow and continuous from the E-BC sealer (Fig. 1c).

Generalized linear mixed model analysis showed significant differences among boron, silicon, and strontium release over time between the two sealer groups. Boron, silicon, and strontium ion concentrations were significantly different over time between S-PRG and E-BC ( $P<0.0001$ ,  $P=0.010$ , and  $P=0.028$ ).

## DISCUSSION

The cumulative ion release of the two sealers was measured in this study because antimicrobial ion release is important in preventing the re-colonization of microorganisms in the root canal system and periapical tissues (22). Neither the cementum nor the smear layer was removed so that the ion elution was maximized from the apex. The cumulative ions released from the sealers are measurable but are not indicative of solubility that exceeds the limit (3%) required in ISO 6876 or ADA 57.

The antimicrobial effects of Boron have been demonstrated on Gram positive (G+) and Gram negative (G-) bacteria in anaerobic environments (17). Boron, as a bacteriostatic agent (17, 23), could help quell the growth of bacteria present in the filled canals if incorporated in an endodontic sealer. Similarly, boron ions eluted from the apex could contribute to the resolution of periapical lesions. Miyaji et al. demonstrated the efficacy of the S-PRG sealer against *E. faecalis*, G+ microbe commonly cultured from secondary endodontic infections (24), and found that, due to its release of antibacterial ions such as boron and strontium, S-PRG sealer exhibited more significant antibacterial effects against *E. faecalis* than a silica-filled sealer (11). Boron also has been associated with anti-inflammatory effects resulting in the prevention of bone loss (25) and the ability to stimulate osteoblastic activity, thereby promoting bone formation (26).

Strontium ions have been linked to enhanced bone formation and strengthening in bone cement containing bioactive glasses substituted with strontium (16). The major role of strontium ions in bone healing appears to be osteoinduction (11). Kusaka et al. reported increased osteogenesis around the S-PRG sealer in a bone implantation study (19). Strontium ions released from S-PRG sealer may promote the differentiation of stem cells into osteoblasts, increasing osteoblastic activity (19). Sasaki et al. found increased levels of strontium ions, as seen in bioglass-containing glass ionomer cement, had no cytotoxicity on osteoblasts and allowed normal cellular proliferation (27). Like boron, strontium also exhibited antimicrobial effects on G+ organisms (15). The ability of strontium ions

to increase the apical bone formation in combination with its antimicrobial properties could enhance the apical healing process post-endodontic treatment (19). Hong et al. found there were no significant differences in bacterial diversity between primary and persistent infections using pyrosequencing, and bacteroidetes was the most abundant phylum in both infections (28). It will be interesting to find out whether boron and strontium ions have an anti-bacteroidetes effect.

The S-PRG sealer released fewer silicon ions over time when compared to the E-BC sealer. Silicon is not known to be antimicrobial but has been shown to increase bone mass (18). Silicon plays a role in collagen synthesis, which contributes to both bone formation and tooth remineralization (20). Silicon also stimulates the osteoblastic production of the extracellular matrix, thereby contributing to the lesion healing process (27), and promoting the mineralization of collagen (29). Silicon ions from E-BC sealer were presumed to originate from the tri/dicalcium silicate cement component. The E-BC sealer had a high amount of silicon ion release, perhaps due to the high value of solubility of the E-BC sealer (21). Table 1 does not show any boron or strontium containing compounds in the E-BC sealer, yet the sealer eluted boron and strontium ions from unidentified sources. While tricalcium silicate sealers produce a more desirable apical seal than other types of sealers (30), the setting time of tricalcium silicate sealers is much longer (>2 hours) compared to that of S-PRG sealer (13 minutes). The quick-setting time should be kept in mind during root canal filling.

In summary, boron and strontium ion release from the root apex in high concentrations over time contributes to antimicrobial action in the S-PRG sealer, and the release of silicon ions assists in bone formation and mineralization effects. A sealer that can release ions with antimicrobial properties after placement may increase the potential for periapical healing and decrease endodontic failure. Future in vivo studies of the effect of the S-PRG sealer on periapical healing are needed to evaluate the clinical benefits of S-PRG sealer's ion release.

## CONCLUSION

The prototype S-PRG sealer released boron and strontium ions in higher cumulative concentrations over 2 weeks compared to the EndoSequence BC sealer. Both the prototype S-PRG and EndoSequence BC sealers released silicon ions, although significantly more were eluted from the EndoSequence BC sealer. Antimicrobial and osteogenic ion release from sealers is expected to positively influence the post-treatment control of microbial infections and improve periapical healing.

## Disclosures

**Conflict of interest:** None declared.

**Ethics Committee Approval:** Not human subject research. (Date: December 15, 2015, Number: 121515-014)

**Peer-review:** Externally peer-reviewed.

**Financial Disclosure:** This publication was supported by NIH UL1 TR001105, the University of New England Office of Sponsored Research and Scholarship, and the Shofu Dental Corporation (Kyoto, Japan).

**Authorship contributions:** Concept – A.B., N.C., T.K.; Design – A.B., N.C., C.M., T.K.; Supervision – C.M., C.P., T.K.; Funding – C.M., C.A., T.K.; Materials – C.M., T.K.;

Data collection &/or processing – A.B., N.C.; Analysis and/or interpretation – A.B., N.C., C.M., C.A., Q.Z., C.P., T.K.; Literature search – A.B., N.C., Q.Z., T.K.; Writing – A.B., T.K.; Critical Review – N.C., C.M., C.A., Q.Z., C.P.

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