Original Article

Effect of Fluoride-incorporated Bioactive Glass Toothpaste on Remineralization of Primary Enamel Lesions: An *In-Vitro* Study

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ABSTRACT

Aims: This study aimed to evaluate the enamel remineralization effect of fluoride-incorporated bioactive glass (F-BG) toothpaste on artificial subsurface caries in primary teeth. **Materials and Methods:** Forty sound primary maxillary incisors were subjected to a demineralizing solution for four days to induce artificial enamel caries. The teeth were randomly divided into four experimental groups (n = 10 per group): Group I, F-BG toothpaste (530 ppm fluoride) (BiominF®); Group II, 0.22% sodium fluoride toothpaste (1000 ppm fluoride) (Colgate®); Group III, 0.32% sodium fluoride toothpaste (1450 ppm fluoride) (Colgate®); and Group IV, deionized water as a control. Over the course of seven days, each specimen was treated with a slurry of the respective toothpaste twice daily, followed by pH cycling to simulate oral conditions. Mineral density (MD) values were measured at depths of 0, 40, 80, and 120 µm using micro-computed tomography (micro-CT) before and after the pH cycling. The percentage of remineralization was calculated based on changes in MD. Statistical comparisons among the groups were made using one-way analysis of variance (ANOVA), followed by post-hoc Bonferroni tests, with a significance level set at $P < 0.05$. **Results:** At depths of 0, 40, and 80 µm, both F-BG toothpaste (Group I) and the 1450 ppm fluoride toothpaste (Group III) demonstrated significantly higher remineralization than the 1000 ppm fluoride toothpaste (Group II) and the control group (Group IV) ($P < 0.05$). No significant difference in remineralization was observed between Group I and Group III ($P > 0.05$). At a depth of 120 µm, none of the test groups showed significant remineralization compared to the control group. **Conclusions:** The fluoride-incorporated bioactive glass toothpaste (530 ppm fluoride) demonstrated remineralization effects on enamel comparable to those of the 1450 ppm fluoride toothpaste in terms of both surface and subsurface enamel restoration in primary teeth. Clinically, this suggests that F-BG toothpaste may be a viable alternative for remineralization therapy in pediatric populations, especially in situations where lower fluoride concentrations are preferred for young children. Further long-term studies are needed to assess the clinical durability and efficacy of F-BG toothpaste in caries prevention and management.

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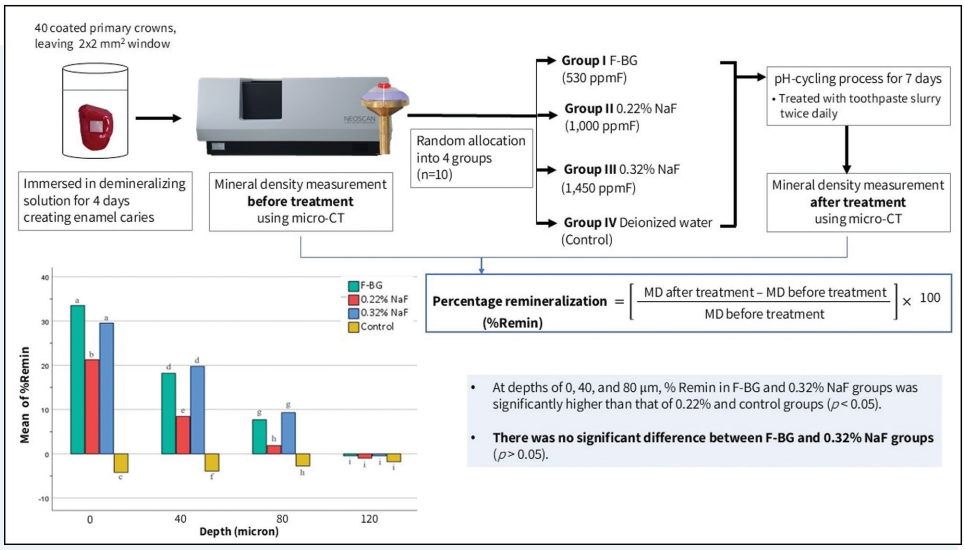

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INTRODUCTION

Dental caries, which results from the gradual demineralization of tooth structure by acid byproducts from bacterial metabolism, is a major oral health problem in children.[1] To control dental caries, fluoride plays an important role in inhibiting demineralization and enhancing remineralization.[2] Fluoride toothpaste is one of the most effective methods for fluoride use in reducing caries; thus, it is recommended that children brush with toothpaste containing at least 1000 ppm fluoride twice a day as a preventive measure.[3] Higher fluoride concentrations in toothpaste provide better protection against tooth decay, making it suitable for use in high-caries risk patients.[4,5] However, the risk of developing fluorosis is increasing, especially in unsupervised children under 6 years of age, due to excessive fluoride ingestion.[6]

Regarding fluorosis, several alternative non-fluoride agents have been developed to enhance the remineralizing efficacy, such as calcium phosphate systems. Bioactive glass (BG), a crystalline calcium phosphate, serves as an extrinsic source of calcium and phosphate ions for the remineralizing process.[7] When BG interacts with saliva, those ions gradually release to form a hydroxyapatite-like layer, particularly in acidic conditions.[8,9] However, the remineralization effect of BG toothpaste on enamel caries was found to be inferior to that of 1000 ppm fluoride toothpaste.[10]

Recent advancements have focused on the incorporation of low-concentration fluoride into BG particles, resulting in fluoride-incorporated bioactive glass (F-BG). As a promising remineralizing agent, F-BG has been used in toothpastes for treating dentin hypersensitivity and initial enamel caries.[8] Several studies in permanent teeth reported that F-BG toothpaste effectively remineralized surface enamel lesions, comparable to 1450 ppm fluoride toothpaste.[11-14] However, surface remineralization alone is insufficient for restoring the structural properties compromised by initial enamel caries. Subsurface remineralization is necessary to strengthen the tooth structure.[7]

Few studies have been conducted on the effects of F-BG toothpaste on subsurface remineralization, particularly on enamel lesions in primary teeth. For young children, using an alternative toothpaste that provides similar caries prevention benefits as higher-fluoride concentration toothpaste, while lowering the risk of fluorosis, could be a more effective and safer option. Therefore, the purpose of this *in vitro* study was to assess the ability of F-BG toothpaste to remineralize surface and subsurface artificial enamel caries in primary teeth. This assessment was based on mineral density (MD) values obtained from micro-computed tomography (micro-CT). We hypothesized that there is no difference in the remineralization effect between F-BG toothpaste and sodium fluoride toothpaste with a fluoride concentration of 1000 ppm or higher.

Materials and Methods

Subjects

The study protocols were approved by the Ethics Committee of Mahidol University, Thailand (MU-DT/PY-IRB 2022/050.2010). Based on the sample size calculation by Farooq *et al.*[11], 10 samples per group were required. This calculation used a significance level of 0.05 with a power of 0.95, computed with G*power version 3.1.9.4.

Forty sound primary incisors were collected by extraction or natural exfoliation and stored in 0.9% normal saline at room temperature until used. Teeth with carious lesions, crack lines, or any enamel defects were excluded.

Specimen preparation

Each tooth had its radicular part removed, and only the coronal part was used. Utility wax and a putty silicone block were prepared for each specimen to facilitate repeated repositioning during the micro-CT scan. The labial surface of the specimen was placed horizontally parallel to the rotation stage.[10] Four reference grooves were made on the labial tooth surface using wax and putty silicone block on the rotation stage for the same position and alignment.[15-17] The specimens were coated with two layers of acid-resistant nail varnish (Revlon Inc., New York, NY), with a 2×2 mm^2 area in the middle third of the labial surface left exposed for treatment.

Demineralization, remineralization solution, and artificial saliva preparation

The two demineralizing solutions and one remineralizing solution were prepared as described by Rirattanapong *et al.*[18] The demineralizing solution 1 (D1) for creating caries lesions comprised 2.2 mM $CaCl_2$, 2.2 mM NaH_2PO_4, and 0.05 M acetic acid, and the pH was adjusted to 4.4 with 1M KOH. Demineralizing solution 2 (D2) to mimic oral conditions in the pH-cycling had the same composition as D1, but the pH was adjusted to 4.7 instead. The remineralizing solution (R) comprised 1.5 mM $CaCl_2$, 0.9 mM NaH_2PO_4, and 0.15 M KCl, and the pH was adjusted to 7.0 using 1 M KOH.

The artificial saliva preparation, which was modified from that proposed by Amaechi *et al.*[19] consisted of 0.65 g/L KCl, 0.058 g/L $MgCl_2$, 0.165 g/L $CaCl_2$, 0.804 g/L K_2HPO_4, 0.365 g/L KH_2PO_4, 2 g/L $NaCO_2CH_3$ cellulose, and deionized water. Artificial saliva was used as a storage medium after lesion formation.

Artificial caries lesion formation

To create caries lesions at depths of 90–110 µm, each specimen was immersed in D1 and placed in an incubator at 37°C (Sheldon Manufacturing, Model 1545, Oregon, USA) for 96 h.[18,20] Following that, it was ultrasonically cleaned in deionized water, gently dried with tissue paper, and maintained in artificial saliva until used.

Grouping and preparation of toothpaste slurry

The specimens were randomly and equally divided into four groups ($n = 10$): Group I, F-BG toothpaste (F-BG – 530 ppm F) (BiominF® kids); Group II, 0.22% sodium fluoride toothpaste (NaF – 1000 ppm F) (Colgate® Minions); Group III, 0.32% sodium fluoride toothpaste (NaF – 1450 ppm F) (Colgate® 3–5 years); and Group IV deionized water (control) [Table 1].

The toothpaste slurry was prepared by mixing deionized water and toothpaste at a 3:1 ratio and stirring with a magnetic stirrer for 20 min.[10] The toothpaste slurries were freshly prepared before use.

pH-cycling process

In order to simulate dynamic pH changes in the oral cavity, a 7-day pH-cycling process was performed. In

Table 1: Toothpaste samples

Group	Tradename	Active ingredient	Manufacturer
I F-BG	BiominF® for kids (strawberry flavor)	Fluoro-calcium phosphosilicate 530 ppmF	BioMin Technologies Ltd., London, UK
II 0.22% NaF	Colgate® kids minions (strawberry gel flavor)	Sodium fluoride 1000 ppmF	Colgate-Palmolive (Thailand) Ltd., Bangkok, Thailand
III 0.32% NaF	Colgate® kids 3–5 years (natural fruity flavor)	Sodium fluoride 1450 ppmF	Colgate-Palmolive (UK) Ltd., Surrey, UK

the daily cycle, the specimens were immersed in D2 for 3 h twice and R for 2 h between D2 immersions and 16 h overnight at 37°C in an incubator. Each specimen was soaked in toothpaste slurry for 2 min twice daily, before the first demineralization and after the second demineralization.[10] After completing the pH-cycling, the specimens were stored in artificial saliva until evaluation.

Remineralization measurement by micro-CT

The measurement was performed twice: before treatment (post-lesion formation) and after treatment (post-pH-cycling) using micro-CT (Neoscan n80, Mechelen, Belgium).[21] The source settings were 75 kV of voltage and 200 µA of current, with a 1-mm-thick aluminum filter used. The image pixel size was 10 µm with a frame average of 4. During the scanning procedure, each specimen was rotated 360° in steps of 0.2°. Two standard hydroxyapatite phantoms with densities of 0.25 and 0.75 gHAp/cm^3 were scanned to calibrate the MD.[10]

The raw scan data, obtained as 255 TIFF files, were reconstructed into three-dimensional (3D) images with a resolution of 2464 × 2464 pixels and a pixel size of 9.96 µm using NRecon software (SkyScan, Antwerp, Belgium). The 3D images were adjusted and aligned with Dataviewer software (SkyScan, Antwerp, Belgium) to match the images taken before and after treatment based on reference grooves and window edges.[11-13] The CTAn software (SkyScan, Antwerp, Belgium) was used to analyze MD (gHAp/cm^3) based on grayscale values obtained from the scanned images. MD values were calculated for each specimen every 40 µm, ranging from 0 to 120 µm in depth. The mean MD change was calculated as the percentage remineralization (%Remin) = 100 × [(MD after treatment − MD before treatment)/MD before treatment].[21]

Intra-examination reliability

Eight samples, representing 20% of the total, were repeatedly analyzed by the same examiner.[10] The reliability of the intra-examination was evaluated using the intraclass correlation coefficient, which was 0.98.

Statistical analysis

The mean MD before treatment and after treatment was compared using the paired samples *t* test. To determine the difference in percentage remineralization among the four depths studied in each group, repeated measures analysis of variance (ANOVA) was used. One-way ANOVA was performed to compare the %Remin among the four groups, followed by the Bonferroni *post hoc* test for multiple comparisons. *P*-values below 0.05 were considered significant. The data were analyzed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA).

Results

Before treatment, there were no significant differences in mean MD among the four groups at all depths ($P > 0.05$). The means and standard deviations in MD before treatment and after treatment and the %Remin for each group are presented in Table 2.

After treatment, the mean MD significantly increased in groups I, II, and III at depths of 0 and 40 µm compared with before treatment. Additionally, groups I and III exhibited a significant increase in MD at a depth of 80 µm. However, at a depth of 120 µm, the test groups demonstrated decreased MD. In the untreated control group, the mean MD after pH-cycling decreased significantly at all depths.

Comparing the mean %Remin among different depths in each group, the test groups demonstrated an increase in %Remin at all depths, except 120 µm, which had the highest %Remin at a depth of 0 µm and then decreased at greater depths. Groups I and III showed significant differences in %Remin among the four depths. However, Group II had significant differences among depths of 0, 40, and 80 µm, but no significant differences between depths of 80 and 120 µm. In contrast, in the control group, the %Remin increased at greater depths, with no significant difference in the %Remin among the four depths.

Table 3 and Figure 1 illustrate the mean %Remin among the groups in each depth. The test groups demonstrated a significantly increased %Remin compared with the control group at depths of 0 and 40 µm ($P \leq 0.001$), whereas the %Remin decreased in the control group at all depths. At depths of 0, 40, and 80 µm, groups I and III had significantly higher %Remin than group II and the control group ($P < 0.05$ and $P < 0.001$ respectively). However, there was no significant difference between group II and the control group at a depth of 80 µm ($P = 0.065$). Comparing groups I and III at each depth demonstrated no significant differences in %Remin ($P > 0.05$). Furthermore, at a depth of 120 µm, the %Remin in the test groups was not significantly different compared with the control group ($P = 1.000$).

Discussion

This study investigated the remineralization effect of F-BG toothpaste on subsurface artificial enamel lesions in primary teeth. After creating artificial enamel caries,

Table 2: Mean mineral density (MD) before and after treatment and the percentage remineralization in the groups

Group	Depth (μm)	*N*	MD (g/cm³) (mean ± SD)		*P* value	Mean % remineralization (mean ± SD)
			Before treatment	After treatment		
I	0	10	0.417 ± 0.062	0.556 ± 0.078	< 0.001*	33.518 ± 6.558[a]
F-BG	40	10	0.760 ± 0.176	0.896 ± 0.196	< 0.001*	18.210 ± 7.990[b]
	80	10	1.118 ± 0.317	1.204 ± 0.342	< 0.001*	7.708 ± 2.920[c]
	120	10	1.367 ± 0.349	1.358 ± 0.336	0.400	− 0.454 ± 2.644[d]
	P value		< 0.001*	0.001*		< 0.001*
II	0	10	0.439 ± 0.075	0.529 ± 0.078	< 0.001*	21.257 ± 7.147[e]
0.22%NaF	40	10	0.786 ± 0.143	0.850 ± 0.151	0.001*	8.452 ± 5.164[f]
	80	10	1.127 ± 0.243	1.146 ± 0.242	0.219	1.869 ± 4.428[g]
	120	10	1.414 ± 0.222	1.399 ± 0.211	0.106	− 0.992 ± 2.003[g]
	P value		< 0.001*	< 0.001*		< 0.001*
III	0	10	0.430 ± 0.088	0.553 ± 0.094	< 0.001*	29.54 ± 5.836[h]
0.32%NaF	40	10	0.782 ± 0.129	0.931 ± 0.116	< 0.001*	19.778 ± 6.618[i]
	80	10	1.213 ± 0.224	1.321 ± 0.205	< 0.001*	9.323 ± 4.244[j]
	120	10	1.511 ± 0.215	1.503 ± 0.205	0.542	− 0.462 ± 2.879[k]
	P value		< 0.001*	< 0.001*		< 0.001*
IV	0	10	0.511 ± 0.086	0.491 ± 0.095	0.041*	− 4.203 ± 5.455[l]
control	40	10	0.821 ± 0.141	0.790 ± 0.145	0.027*	− 3.899 ± 4.880[l]
	80	10	1.102 ± 0.178	1.075 ± 0.197	0.038*	− 2.747 ± 3.604[l]
	120	10	1.332 ± 0.251	1.308 ± 0.245	0.045*	− 1.787 ± 2.626[l]
	P value	10	< 0.001*	< 0.001*		0.645

*Different superscript letters indicate significant difference ($P < 0.05$)

P values in the column were determined by paired *t* test

P values in the row were determined by repeated-measures analysis of variance

Multiple comparisons used Bonferroni *post hoc* test

Table 3: Comparison mean percentage remineralization between groups at each depth

Depth (μm)	Group	*N*	% Remineralization (mean ± SD)
0	I F-BG	10	33.518 ± 6.558[a]
	II 0.22% NaF	10	21.257 ± 7.147[b]
	III 0.32% NaF	10	29.54 ± 5.836[a]
	IV control	10	− 4.203 ± 5.455[c]
40	I F-BG	10	18.210 ± 7.990[d]
	II 0.22% NaF	10	8.452 ± 5.164[e]
	III 0.32% NaF	10	19.778 ± 6.618[d]
	IV control	10	− 3.899 ± 4.880[f]
80	I F-BG	10	7.708 ± 2.920[g]
	II 0.22% NaF	10	1.869 ± 4.428[h]
	III 0.32% NaF	10	9.323 ± 4.244[g]
	IV control	10	− 2.747 ± 3.604[h]
120	I F-BG	10	− 0.454 ± 2.644[i]
	II 0.22% NaF	10	− 0.992 ± 2.003[i]
	III 0.32% NaF	10	− 0.462 ± 2.879[i]
	IV control	10	− 1.787 ± 2.626[i]

Different superscript letters indicate significant difference ($P < 0.05$), determined by one-way analysis of variance with Bonferroni *post hoc* test

there were no significant differences in mean MD among the prepared groups at every depth. This value served as a baseline before treatment. The teeth were then treated using pH-cycling to assess the remineralizing efficacy of the toothpastes.[22,23] Following pH-cycling, the control group without treatment had a significant decrease in MD and %Remin at all depths. This result was in line with those of Ten-Cate *et al.*[24] who found a reduction in mineral content within the surface and body of the lesion after pH-cycling. Conversely, the test groups demonstrated an increase in MD and %Remin at all depths, except 120 μm. The highest %Remin was found at the superficial level, which decreased at deeper levels after treatment. This was similar to the observations of studies on other fluoride toothpastes, indicating that the gains in MD decreased as the depth increased.[16,21] This is likely due to the low fluoride amount that diffuses to the lower depths.[25]

The NaF toothpaste with different concentrations, 0.32% NaF (1450 ppm F) and 0.22% NaF (1000 ppm F), demonstrated different remineralization efficacies. The 0.32% NaF toothpaste had a significant increase in MD and %Remin at depths of 0, 40, and 80 μm. This finding was consistent with that of a previous study, which showed effective remineralization by 1450 ppm fluoride toothpaste up to approximately 70 μm deep, as

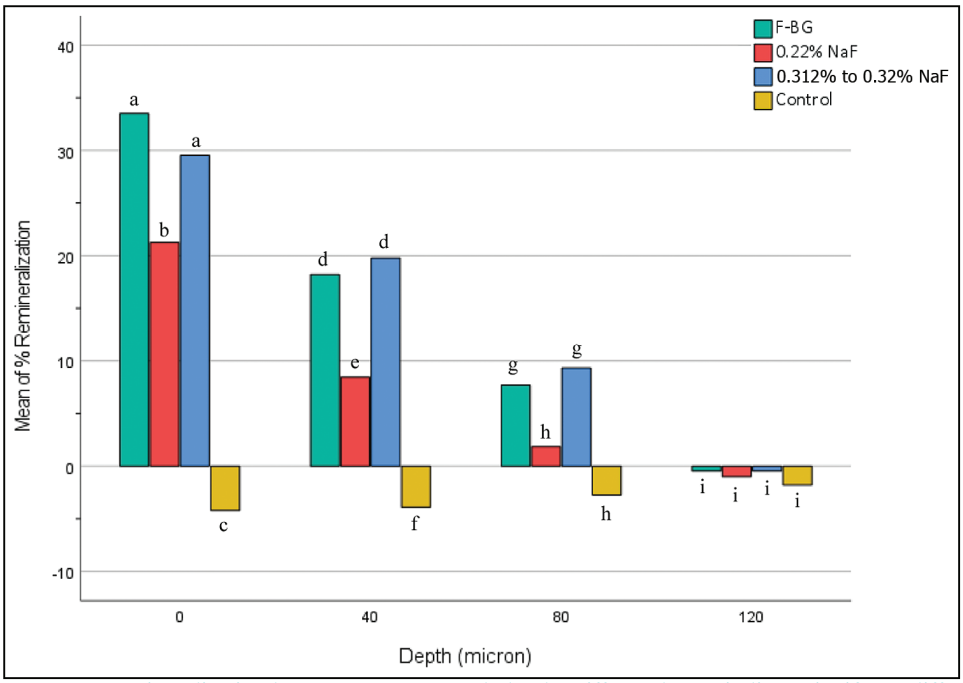

Figure 1: The mean percentage remineralization between groups at each depth. Different letters indicate significant differences between groups (one-way analysis of variance with Bonferroni *post hoc* test, $P < 0.05$)

determined by cross-sectional hardness analysis.[26] In contrast, the 0.22% NaF toothpaste had a significant increase in MD and %Remin at depths of 0 and 40 µm, which was in line with the findings of a previous study demonstrating that 1100 ppm fluoride toothpaste increased the mineral concentration to a lesion depth of 40 µm.[27] Moreover, the %Remin of 0.22% NaF toothpaste was significantly lower than that of 0.32% NaF toothpaste. This could be explained by different fluoride concentrations. A previous study reported that high-fluoride toothpaste led to greater and deeper increases in the mineral volume within the lesion body compared with the lower fluoride concentration toothpaste.[24] Furthermore, the fluoride concentration had a direct effect on the mineral uptake of lesions, with a higher fluoride level increasing the mineral uptake.[23,24]

The F-BG toothpaste, which contained different types and concentrations of fluoride, demonstrated a significant increase in MD and %Remin at depths of 0, 40, and 80 µm. The F-BG toothpaste consisted of 530 ppm fluoride concentration in the form of fluoro-calcium phosphosilicate particles as its active ingredient.[11,28] Despite the low fluoride concentration in F-BG toothpaste, it effectively promoted remineralization to a depth of 80 µm. This might be due to the F-BG particles providing an extrinsic source of calcium and phosphate ions. There is evidence that F-BG toothpaste had elevated levels of calcium and phosphate ions released in the solutions.[29] The bioavailability of calcium, phosphate, and fluoride ions enhances their diffusion to subsurface lesions, followed by precipitation.[7,11,29-31] Moreover, this finding was consistent with that of a study of F-BG particles (BiominF® powder) in paste form, which found a new layer of crystal-like structures rich in calcium and phosphate formed on the demineralized enamel surface, along with a smooth area in the subsurface lesion.[32]

The %Remin of F-BG toothpaste (530 ppm F) was significantly higher than that of 0.22% NaF (1000 ppm F) toothpaste at depths of 0, 40, and 80 µm. However, a previous study indicated that the low fluoride (500 ppm F) or BG toothpaste had a lower remineralization effect than the 1000 ppm fluoride toothpaste.[10] The remineralization effect was improved in the F-BG toothpaste, which adds a low fluoride level to BG particles. There were no significant differences in %Remin between F-BG and 0.32% NaF toothpaste at all depths. The remineralizing efficacy of F-BG toothpaste might be attributed to the synergistic effect of combining fluoride with crystalline calcium phosphate particles.[30,33,34] This mechanism was supported by a previous study that demonstrated F-BG toothpaste had a significantly greater impact on enamel remineralization compared to toothpaste containing only BG.[34] F-BG particles in toothpaste can interact with saliva, allowing the glass to degrade and gradually release calcium, phosphate, and

fluoride ions. Adequate levels of these ions promote their precipitation and the formation of an apatite layer.[29,34-38] Additionally, the degradation process of BG elevates the environmental pH as a neutralizing effect, which enhances ion precipitation.[29,36,37] Fluoride in BG promotes nucleation and leads to the formation of fluorapatite, which is less soluble and more resistant to acidic environments.[9,29,38] These properties might contribute to enhancing remineralization and inhibiting the demineralization process.

Regarding the effect on the surface level, the F-BG toothpaste (530 ppm F) had no significant differences in %Remin compared with 0.32% NaF (1450 ppm F) toothpaste. Several studies on permanent teeth have revealed that the F-BG toothpaste had the same remineralization as 1450 ppm fluoride toothpaste, which resulted in increased enamel surface microhardness and a smoother superficial surface.[11,13,14] Furthermore, our study demonstrated that F-BG and 0.32% NaF toothpaste also had a similar remineralization effect at depths of 40 and 80 µm, respectively. These results imply that F-BG toothpaste remineralized the surface and subsurface artificial enamel lesions in primary teeth.

In this *in vitro* study, the pH-cycling model could not exactly mimic the real intraoral environment, which includes other factors such as salivary composition, the presence of microorganisms, and oral fluid dynamics. Although these factors can influence the demineralization and remineralization processes, our study used a method design according to previous studies showing effectiveness in evaluating the remineralization effect.[10,39] However, additional clinical studies are required to confirm the long-term effectiveness of F-BG toothpaste in young patients.

Conclusion

The F-BG toothpaste had efficacy in remineralizing artificial enamel caries on surface and subsurface levels of primary teeth. The remineralization effect of the F-BG toothpaste was similar to that of 1450 ppm fluoride toothpaste. Therefore, the F-BG toothpaste might be considered as a safer alternative for young children at high risk of caries or those with initial enamel caries.

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Conflicts of interest

There are no conflicts of interest.

Authors contributions

PR formulated the research question and designed the framework with VY and NK. NK conducted the experiments, and all authors participated in data analysis. NK and PR wrote and revised the manuscript. All authors approved the final version of the manuscript.

Ethical policy and Institutional Review board statement

This study was approved by the Ethics Committee of Mahidol University, Thailand (MU-DT/PY-IRB 2022/050.2010).

Patient declaration of consent

Nil.

Data availability statement

The additional data of this study are available on request from Dr. Nuttamon Katkanchano at nuttamon.katk@gmail.com.

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