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ORIGINAL ARTICLE

Fluoride and calcium release from peppermint-flavored fluoride varnish containing dicalcium-phosphate-dihydrate coated with xylitol

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KEYWORDS

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Abstract Bakground: Fluoride varnish with high initial fluoride and calcium release can help patients with high-risk caries. Ample quantities of free fluoride and calcium ions in the oral cavity can enhance enamel remineralization. This study aimed to investigate the effect of dicalcium phosphate dihydrate coated with xylitol (DCPD-xylitol), in fluoride varnish, on the release of fluoride and calcium ions in the oral cavity.

Materials and methods: DCPD powder with xylitol was synthesized by preparing a 60% xylitol solution and mixed it with DCPD solution. The mixture was stirred for 1 h at room temperature and dried at 80 °C for 18 h to reduce the water content. Then, the powder was used in the formulation of peppermint-flavored fluoride varnish as an active agent. The amounts of fluoride and calcium ion released in deionized water at 37 °C for 6 h were assessed with an ion-selective electrode. The cumulative fluoride and calcium ion release data were analyzed using one-way analysis of variance (ANOVA) and the post hoc Tukey test with $\alpha = 0.05$.

Results: The results showed that the addition of DCPD coated with xylitol provided better bioavailability of the ions than DCPD without coating. Peppermint-flavored fluoride varnish (PFFV) with DCPD-xylitol 1% gave the highest fluoride ion release (296.90 mg/L) compared to

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the varnishes with other xylitol concentrations and the positive control. In contrast, PFFV DCPD-xylitol 5% afforded the highest calcium ion release at 111.20 mg/L.

Conclusions: This study concluded that xylitol affects the bioavailability of free fluoride and calcium ions in varnishes. However, the efficacy of fluoride and calcium uptake in enamel and under different in vitro media conditions requires further investigation.

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1. Introduction

Early childhood caries is one of the many public health issues that impacts infants and preschool children worldwide. Untreated caries result in incremental destruction of the crowns of teeth, frequently followed by extreme pain and suffering that affect the quality of life and cause other health problems (Achmad et al., 2020; Bıcak and Akyuz, 2018; Chen et al., 2018). The key to solving caries is maintaining the complex equilibrium of the demineralization-remineraliza tion reaction in the oral cavity by supplying bioavailable tooth-forming minerals (Forssten et al., 2010). In dental health, fluoride has long been known to play a vital role in inhibiting caries. It is commonly used in many forms, such as water fluoridation, toothpaste, mouthwash, and fluoride varnish (Petersen and Ogawa, 2016).

Fluoride varnish has been acknowledged to effectively prevent early childhood caries. Along with its ease of application and acceptance by children, the presence of fluoride increases the resistance of enamel dissolution by acid by forming fluorapatite ($CA_{10}(PO_4)6F_2$) (Rugg-Gunn, 2013). When fluoride is applied to teeth, a calcium fluoride-like layer precipitate (CaF_2) is formed on the enamel surface. This serves primarily as a mineral reservoir and can partly act as a physical barrier that prevents interaction between acids and the enamel (Shahmoradi et al., 2017). However, fluoride alone is not sufficient to prevent demineralization and replace minerals lost from tooth enamel. Every two fluoride ions require ten calcium ions and six phosphate ions to form one fluorapatite molecule (Dai et al., 2019). When a topical fluoride product is applied, the lack of bioavailable calcium and phosphate ions in the oral cavity can be the limiting factor for fluoride to work optimally. Even though saliva contains calcium and phosphate ions, the fluoride varnish mixture still needs an active ingredient, such as calcium phosphate. Calcium phosphate can increase remineralization by exerting a synergistic effect between fluorapatite-forming elements (Dorozhkin, 2009).

Calcium phosphates are widely used as biomaterials because of their good bioactivity and biocompatibility. They are commonly used in bone fillers, drug delivery systems, coating materials, etc., in the field of bone tissue and dentistry (Eliaz and Metoki, 2017). Dicalcium phosphate dihydrate (DCPD) is a calcium phosphate with high solubility that can deliver bioavailable calcium and phosphate. The chemical formula is $CaHPO_4{\cdot}2H_2O$, and the mineral is known as brushite (Mandel and Tas, 2010). DCPD and octacalcium phosphate (OCP) are precursors of fluorapatite formation (Boanini et al., 2010). Research has shown that saliva solutions supersaturated with DCPD and OCP facilitate the remineralization of dentine (Tschoppe et al., 2009). Besides being dissolved intra-orally and increasing the calcium ions in saliva, another study showed that calcium ions in DCPD also acted as a fluoride carrier that can increase fluoride absorption in artificial enamel caries in primary bovine teeth to enhance remineralization (Rirattanapong et al., 2016). Supplying bioavailable fluoride, calcium, and phosphate ions in dental varnish can be a promising treatment for patients suffering from hyposalivation and in the combined treatment of dental caries and hyposalivation. However, the mechanism of fluoride and calcium ion release using DCPD in fluoride varnish has not been studied so far.

Embrace™ Varnish (5% NaF with CXP™) from Pulpdent Corporation (Watertown, MA) claimed that its varnish has ten times higher fluoride release over 4 h than the other fluoride varnish products. The addition of CXP™ technology (xylitol-coated calcium and phosphate) allegedly drives the long-lasting properties of this varnish. Saliva dissolves the xylitol coating of the permeable resin matrix while calcium and phosphate ions react continuously with fluoride ions to form fluorapatite in the teeth (The Editors, 2012). A study proved Embrace™ Varnish's claim through a comparative fluoride ion release test with other fluoride varnish products: Duraphat® (Colgate Palmolive, New York, NY), Vanish™ (3 M ESPE, St. Paul, MN), and Enamel Pro® Varnish (Premier Dental, Plymouth Meeting, PA, USA) (Milburn and Henrichs, 2015). Through complex interactions, xylitol also acts as a calcium carrier for remineralization of teeth due to the permeability between xylitol and enamel, which increases calcium absorption. Thus, xylitol can promote the remineralization of deeper layers of demineralized enamel by improving the movement and accessibility of calcium ions (Chukwuma and Islam, 2017).

Fluoride varnish with a high initial fluoride and calcium release can help patients with high-risk caries. Ample quantities of free fluoride and calcium ions in the oral cavity with can enhance enamel remineralization. Because of its good antibacterial activity against *Streptococcus mutans*, the selection of peppermint essential oil as a flavor may increase the varnish efficacy (Sreevidhya and Geetha, 2014). This study aims to investigate the combined effect of xylitol and dicalcium phosphate dihydrate on fluoride and calcium ion release from peppermint-flavored fluoride varnish.

2. Materials and methods

2.1. Synthesis of Xylitol-Coated DCPD

The first step was to prepare a 60% xylitol solution by weighing 6 g of xylitol powder (Nacalai, Japan) and dissolving it in 3 g of deionized water. Thereafter, 1.3 g of the xylitol solution was mixed with 31.9 g of dicalcium-phosphate-dihydrate

powder (Merck KGaA, German) and 36.1 g of deionized water. The mixture was stirred for 1 h at room temperature and dried at 80 °C for 18 h to reduce the water content. DCPD powder with xylitol was used. This method is based on Patent US8790707B2 (Rusin et al., 2014).

2.2. Peppermint-Flavored fluoride varnish (PFFV) formulation as base formula

Using a glass beaker closed with aluminum foil, a combination of Foral AX-E fully hydrogenated rosin powder (Eastman, US), ethanol (Merck KGaA, Germany), and peppermint flavor oil (LorAnn Oils, Lansing, Michigan) was magnetically stirred at 240 rpm, at room temperature, until it became homogeneous (3 h). Natrium fluoride powder (Merck KGaA, Germany) was added to the mixture and stirred for 1 h. This formulation made a total mix of as much as 100 g in gel form with no by-product, as shown in Table 1. In addition, this formulation was used as a control varnish.

2.3. Fluoride varnish formulation with DCPD and DCPD-Xylitol

Starting with the PFFV formulation, a combination of fully hydrogenated rosin powder (Foral AX-E, Eastman, US), ethanol (Merck KGaA, Germany), and peppermint flavor oil (LorAnn Oils, Lansing, Michigan), as shown in Table 1, was mixed until homogenous. Thereafter, natrium fluoride (Merck KGaA, Germany) was added to the mixture and stirred for 1 h. Calcium phosphate powder (DCPD or DCPD-xylitol) was added to the mixture and stirred again for 1 h. This method created a cumulative mix of 100 g in gel form with no by-product for each varnish formulation. The concentration of DCPD-xylitol was varied as 1%, 2%, 3%, 4%, and 5%, referring to Patent US 20180116914A1, which states that a range of 1–5% is the preferred concentration range for calcium phosphate in manufacturing fluoride varnish (Allred and Kasteler, 2014). The PFFV formulation was used as a varnish control in this study.

2.4. Fluoride ion release test

Each varnish formulation sample (0.05 g) was applied at the bottom of a 50 mL transparent plastic polypropylene cup. Twenty-five milliliters of deionized water was then added to the plastic cup and incubated for 30 min at 37 °C. After 30 min, the test solution was moved to another container, and the sample cup was filled with fresh deionized water and incubated again for 30 min. The fluoride ions in the test solution were measured using an ion-selective fluoride electrode (LaquaAct pH 130, HORIBA, Japan) with 25 mL of TISAB solution to strengthen the ion reading. The ion readings were performed three times. The same procedure was repeated to measure the release of fluoride ions for 6 h.

2.5. Calcium ion release test

Similar to the fluoride ion release test, 0.05 g of each varnish formulation sample was applied to the bottom of a 50 mL transparent plastic polypropylene cup. Twenty-five milliliters of deionized water was then added to the plastic cup and incubated for 30 min at 37 °C. After 30 min, the test solution was moved to another container, and the sample cup was filled with fresh deionized water and incubated again for 30 min. The calcium ions in the test solution were measured using an ion-selective calcium electrode (LaquaAct pH 130, HORIBA, Japan) with 12.5 mL of ISA solution to strengthen the ion reading. The ion readings were performed three times. The same procedure was repeated to measure the release of calcium ions over 6 h.

2.6. Data analysis

The cumulative fluoride and calcium ion release data were analyzed for normality and equality of variance and the means were compared using a one-way ANOVA with Tukey post hoc test using SPSS version 23.0 software (; SPSS, Chicago, IL, USA). The significance level was set at $\alpha = 0.05$ for all statistical tests.

3. Results

3.1. Effect of adding DCPD and xylitol on amount of fluoride ions released

The cumulative results of fluoride ion release are expressed in mg/L units, as shown in Fig. 1, with detailed data in Table 2.

All samples tested were found to have a detectable release of fluoride ions. PFFV DCPD-xylitol had the highest cumulative release of fluoride ions after 360 min compared to the formula without xylitol. PFFV DCPD-xylitol 1% had the highest ion fluoride release, reaching 296.90 mg/L. PFFV DCPD-Xylitol 2% had the second highest release of 279.87 mg/L, followed by PFFV DCPD-Xylitol 3% (269.99 mg/L), PFFV

Table 1 Fluoride Varnish Composition (%).

Components	Percent Composition						
	PFFV	PFFV DCPD	PFFV DCPD-Xylitol				
			1%	2%	3%	4%	5%
Ethanol	22.5	22	22	22	22	22	22
Fully Hydrogenated Rosin	70	67.5	69.5	68.5	67.5	66.5	65.5
Natrium Fluoride	5	5	5	5	5	5	5
Peppermint Oil	2.5	2.5	2.5	2.5	2.5	2.5	2.5
DCPD	–	3	–	–	–	–	–
DCPD-Xylitol	–	–	1	2	3	4	5

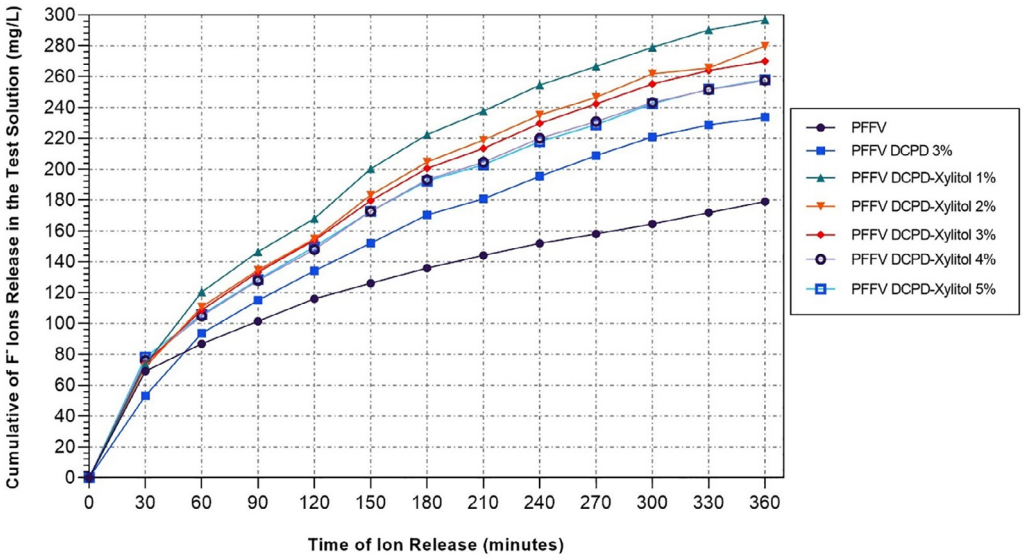

Fig. 1 Correlation Between Addition of DCPD and Xylitol on Amount of Fluoride Ions Released.

Table 2 Cumulative Fluoride Ion Release (mg/L) from the Varnishes.

	30 minutes	60 minutes	90 minutes	120 minutes	150 minutes	180 minutes
PFFV	69.10 [a]	86.80	101.51	116.04	126.07	135.90
PFFV DCPD 3%	53.14	93.62	114.90	134.17	152.00	170.33
PFFV DCPD-Xylitol 1%	73.46 [a,b]	120.41	146.41	168.07	200.24	222.43
PFFV DCPD-Xylitol 2%	71.87 [a,b]	110.79 [a]	134.54 [a]	154.86 [a]	183.30 [a]	204.61 [a]
PFFV DCPD-Xylitol 3%	74.03[b,c]	108.73 [a,b]	133.26 [a,b]	153.98 [a]	179.60 [a,b]	200.52 [a]
PFFV DCPD-Xylitol 4%	75.94[b,c]	104.80[b]	127.85[b]	147.89[b]	172.65[b]	193.21[b]
PFFV DCPD-Xylitol 5%	78.18[c]	105.80 [a,b]	128.49 [a,b]	149.75 [a,b]	172.79[b]	192.30[b]
	210 minutes	**240 minutes**	**270 minutes**	**300 minutes**	**330 minutes**	**360 minutes**
PFFV	144.12	151.88	158.03	164.50	171.83	178.95
PFFV DCPD 3%	180.79	195.7	208.6	221.00	228.5	233.68
PFFV DCPD-Xylitol 1%	237.71	254.43	266.71	278.96	290.24	296.90
PFFV DCPD-Xylitol 2%	218.82 [a]	235.18 [a]	250.35	261.75 [a]	276.00	279.87
PFFV DCPD-Xylitol 3%	213.51 [a]	229.78 [a]	242.37	255.22 [a]	264.05	269.99
PFFV DCPD-Xylitol 4%	204.54[b]	220.02[b]	230.94 [a]	243.15[b]	251.59 [a]	257.62 [a]
PFFV DCPD-Xylitol 5%	205.97[b]	220.83[b]	231.83 [a]	242.50[b]	251.83 [a]	258.00 [a]

Similarly, marked in the same column are not significantly different ($p > 0.05$, ANOVA with Tukey post hoc).

DCPD-Xylitol 5% (258.00 mg/L), PFFV DCPD-Xylitol 4% (257.62 mg/L), PFFV DCPD 3% (233.68 mg/L), and PFFV (as positive control; 178.95 mg/L) in succession. The results show that these samples had a significantly different cumulative release of fluoride ions at each test time, except for PFFV DCPD-xylitol 4% and 5%, with a similar average fluoride ion release at each test time.

3.2. Effect of adding DCPD and xylitol on Amount of calcium ions released

The cumulative results of calcium ion release are shown in Fig. 2, with details in Table 3. All samples tested were found to have a detectable release of calcium ions. The graph shows that PFFV DCPD-xylitol 5% had the highest calcium ion release, reaching 111.20 mg/L, followed by PFFV DCPD-xylitol 4% (101.63 mg/L), PFFV DCPD 3% (93.24 mg/L), PFFV DCPD-xylitol 3% (91.5 mg/L), PFFV DCPD-xylitol 2% (80.25 mg/L), and PFFV DCPD-xylitol 1% (71.61 mg/L) in succession. The results show that these samples had a significantly different cumulative release of fluoride ions at each test time.

4. Discussion

In the first stage of the research, a comparative test was conducted to determine the amount of fluoride ions released from peppermint flavored-fluoride varnish (PFFV) as the base formulation. Variations were performed with the addition of DCPD and DCPD coated with xylitol to peppermint-

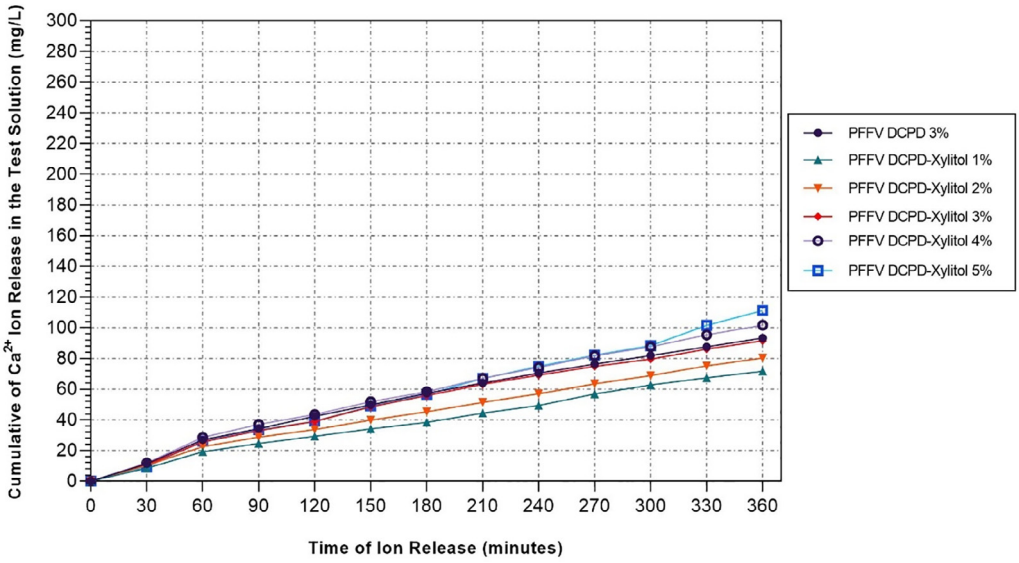

Fig. 2 Correlation Between Addition of DCPD and Xylitol on Amount of Calcium Ions Released.

Table 3 Cumulative Calcium Ion Release (mg/L) from The Varnishes.

	30 minutes	60 minutes	90 minutes	120 minutes	150 minutes	180 minutes
PFFV DCPD 3%	11.38	26.94	34.28	42.33	49.76 [a]	57.18 [a]
PFFV DCPD-Xylitol 1%	8.41	19.08	24.61	29.17	34.04	38.31
PFFV DCPD-Xylitol 2%	10.16 [a]	22.55	28.63	33.70	39.74	45.20
PFFV DCPD-Xylitol 3%	10.50 [a]	25.61 [a]	32.96 [a]	38.86 [a]	48.44[b]	55.80[b,c]
PFFV DCPD-Xylitol 4%	11.81	28.48	36.95	43.42	51.80	58.28[c]
PFFV DCPD-Xylitol 5%	9.35	26.12 [a]	33.46 [a]	39.12 [a]	48.96 [a,b]	56.52 [a,b]
	210 minutes	**240 minutes**	**270 minutes**	**300 minutes**	**330 minutes**	**360 minutes**
PFFV DCPD 3%	64.04 [a]	70.39 [a]	76.23	81.80	87.61 [a]	93.24 [a]
PFFV DCPD-Xylitol 1%	44.33	49.35	56.72	62.63	67.27	71.61
PFFV DCPD-Xylitol 2%	51.34	56.87	63.36	68.76	75.09	80.25
PFFV DCPD-Xylitol 3%	63.12 [a]	69.06 [a]	74.75	79.56	86.07 [a]	91.50 [a]
PFFV DCPD-Xylitol 4%	67.10[b]	74.05[b]	81.66 [a]	87.64 [a]	95.36	101.63
PFFV DCPD-Xylitol 5%	66.95[b]	74.76[b]	82.08 [a]	88.29 [a]	101.56	111.20

Similarly, marked in the same column are not significantly different ($p > 0.05$, ANOVA with Tukey's post-hoc test).

flavored fluoride varnish, along with concentration variations. Fluoride varnish with the addition of DCPD provides a more significant release of fluoride ions because of reduced hydrogenated rosin in its formulation, resulting in reduced final product viscosity. Under these conditions, the fluoride ions diffuse faster in deionized water. The addition of calcium phosphate to fluoride varnish formulations can be problematic because of the unfavorable interactions between calcium, fluoride, and phosphate. These ions can form poorly soluble phases in the varnish during storage and distribution, and can decrease the bioavailability of ions when the varnish is applied in the oral cavity (Cochrane et al., 2014). However, the data showed that the bioavailability of fluoride ions in the test solution remained good. From this test, it can be seen that the addition of modified calcium phosphate provides better bioavailability than DCPD without modification. However, the mechanism of fluoride release is not yet known and requires further investigation.

In contrast with the fluoride test, higher calcium ion release was correlated with a higher concentration of DCPD-xylitol. Xylitol contains a tridentate ligand [$(H–C–OH)_3$] that can react with polyvalent ions such as calcium ions; thus, it can compete with water molecules for the primary calcium hydration layer to form a "xylitol-calcium" complex. This complex interaction leads to stabilization of salivary calcium phosphate systems (Mäkinen, 2000). This process occurred during the synthesis of DCPD-xylitol, which was stabilized by the fluoride reaction in the varnish. When the varnish was submerged in deionized water, the dissolution of xylitol in deionized water allowed the calcium ions to diffuse out.

5. Conclusions

The addition of modified dicalcium phosphate dihydrate with xylitol provided better bioavailability of fluoride than DCPD without xylitol. The higher the concentration of DCPD-xylitol, the higher the calcium release. Despite the fact that xylitol affects the bioavailability of fluoride and calcium ions from the varnishes, this research still needs further investigation. Further tests using artificial saliva, which illustrate the actual condition of the oral cavity, should be considered in future investigations. Additional studies should explore the efficacy of fluoride and calcium uptake in enamel after the application of fluoride varnish. Because the fluoride reservoir in the tooth structure dissolves at lower pH, the output of fluoride varnish with variation of the pH may be of interest.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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