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Effect of fluoride gels supplemented with nano-sized sodium trimetaphosphate on enamel remineralization *in situ*

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ABSTRACT

Objectives: This study evaluated the effect of fluoride gels supplemented with nano-sized sodium trimetaphosphate (TMP) on remineralization of artificial caries lesions in situ.
Materials and methods: Bovine enamel blocks ($n = 160$) with chemically-induced caries-like lesions were randomly distributed into four groups: Placebo (without F and TMP – negative control), 9000 μg F/g (9000F – positive control), 4500 μg F/g + 5 % micrometric TMP (4500F+5 % TMPmicro), and 4500 μg F/g + 5 % nano-sized TMP (4500F+5 %TMPnano). Ten volunteers used palatal devices containing 4 demineralized enamel blocks for 3 days, following a double-blind and crossover protocol. Two enamel blocks were removed immediately after gel application to determine calcium fluoride (CaF_2) formed. After each phase, the samples were analyzed for the percentage of surface hardness recovery (%SHR), cross-sectional hardness (ΔKHN), and CaF_2 retained on enamel. The data were submitted to one-way (%SHR and ΔKHN) or two-way (CaF_2), repeated-measures ANOVA, followed by Student-Newman-Keuls test ($p < 0.05$).
Results: The highest %SHR was observed for 4500F+5 %TMPnano gel, followed by 4500F+5 %TPMmicro, 9000F, and Placebo, with significant differences among all groups. An inverse pattern was verified for ΔKHN, with the highest and lowest values achieved by the Placebo and 4500+5 %TMPnano groups, respectively. Regarding CaF_2 formed, the highest concentration was observed in the 9000F group. For CaF_2 retained, no significant differences were observed among all fluoride-containing gels.
Conclusion: The low-fluoride gel containing TMP led to significantly higher remineralization rates than a conventional gel containing twice as much fluoride; nano-sized TMP resulted in enhanced remineralization compared with micrometric particles.
Clinical significance: The experimental formulation significantly outperformed the conventional fluoride gel in promoting enamel remineralization. These findings suggest a promising and safer alternative to current topical fluoride therapies, with important implications for caries prevention, both for private practice and in public health programs.

1. Introduction

Dental caries is a chronic, multifactorial, and dynamic disease, characterized by a diet-biofilm misbalance, resulting in the progressive mineral loss of dental hard tissues [1,2]. Despite dental caries still affects several populations worldwide [3], a substantial decline in its prevalence has been observed over the years [4]. The widespread use of self- or professional-applied fluoridated vehicles is one of the main reasons to justify such a decline, due to fluoride's ability to prevent the onset and development of caries lesions, by reducing the enamel solubility in acid media, promoting enamel remineralization, and harming the use of glucose by bacteria [5].

Amongst the modalities of professionally-applied fluoridated vehicles, fluoride gels can be regarded as one of the most effective caries

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preventive measures, by reducing 20 % and 28 % of caries lesions development in primary and permanent teeth, respectively [6,7]. However, despite the proven benefits, the indiscriminate use of fluoride gels deserves attention, since the high fluoride levels in these products may lead to acute toxicity [8]. To minimize risks from this source, alternatives have been proposed, including the reduction of fluoride concentration in these products [9,10]. Other alternatives include the addition of calcium and phosphate salts to fluoridated products. Sodium trimetaphosphate (TMP) is a cyclic phosphate that has been added to fluoridated products such as gels, varnishes, mouthwash solutions, and dentifrices, promoting synergistic effects on enamel de- and re-mineralization [11,12] and erosive tooth wear [13]. Several in vitro, in situ and in vivo studies provided the basis for the comprehension of the mechanisms by which interfere with tooth mineral dynamics, which are mainly associated to its strong affinity for hydroxyapatite, which allows TMP to adsorb to enamel surfaces, forming a semi-permeable layer that alters surface energy and charge distribution [14,15]. This favors the attraction and retention of calcium, phosphate, and fluoride ions, which are gradually released under acidic conditions, contributing to mineral redeposition within the lesion body [14–16]. Moreover, TMP can increase fluoride uptake and diffusion by modulating enamel permeability and stabilizing less soluble mineral phases, such as fluoridated apatite [17].

In order to enhance the effects of products containing TMP and considering the above-mentioned results, studies with nano-sized TMP have been conducted. A 1000 μg F/g dentifrice containing nano-sized TMP reduced the enamel demineralization [18,19] and enhanced the remineralization process in situ [16]. This dentifrice was also shown to be more effective against erosive tooth wear than formulations with micrometric TMP or without TMP [20]. The association between fluoride and nano-sized TMP was also tested for fluoride gels containing 1 % NaF, which promoted a similar enamel remineralization rate compared with the positive control (2 %NaF) in vitro [21]. Moreover, the gel containing nano-sized TMP showed a superior protective effect on erosive tooth wear when compared to the positive control [22].

Considering the promising results of the association of nano-sized TMP with F and the limitations inherent to in vitro protocols, this study aimed to evaluate the effect of fluoride gels supplemented with nano-sized TMP on enamel remineralization in situ. The study's null hypotheses were that the remineralizing effect of the fluoride gels would not be affected by the addition of TMP, and that particle (i.e., micrometric or nanosized) size would not influence the parameters analyzed.

2. Material and methods

2.1. Ethical aspects and inclusion criteria

This study was reviewed and approved by the Human Ethics Committee of the School of Dentistry, Araçatuba, São Paulo State University (CAAE: 36.353.320.0.0000.5420). All participants received written and verbal instructions on the research protocol, as well as signed an informed consent statement before the beginning of the study. Ten subjects aged 20-35 years, living in Araçatuba-SP (Brazil), were included in the study. The inclusion criteria involved participants in good general and oral health, who presented normal salivary flow and did not use fixed orthodontic appliances, cigarettes, or drugs that could interfere with the formation of the dental biofilm [12].

2.2. Experimental design

This was a double-blind and crossover in situ study performed in four phases of 3 days each, with a 7-day washout period. Sample size ($n = 8$) was determined with data from a pilot study with 4 subjects assessing the percentage of surface hardness recovery as the primary response variable, considering α-error of 5 %, β-error of 10 %, minimum detectable difference of 8.5, and standard deviation of 4.7. Assuming a 20 % drop-out rate, the sample size was established at 10 subjects. The participants wore palatal appliances with four demineralized bovine enamel blocks each and were randomly divided into 4 groups: Placebo (without F or TMP), 9000 μg F/g (9000F), 4500 μg F/g + 5 % micrometric TMP (4500F+5 %TMPmicro), and 4500 μg F/g + 5 % nano-sized TMP (4500F+5 %TMPnano). Immediately after gel application, two blocks were removed for the analysis of enamel CaF_2 formed. After a 3-day experimental period, surface hardness was again assessed (SH_2) for analysis of mineral gain, evaluated in terms of percentage of surface hardness recovery (%SHR). The integrated loss of subsurface hardness (ΔKHN) and the concentration of CaF_2 retained were also determined.

2.3. Preparation of enamel blocks and induction of subsurface lesions

Bovine lower incisors were kept in a formaldehyde solution of 2 % for 30 days [23]. The enamel blocks (4 × 4 × 2 mm) were obtained from tooth crowns (Fig. 1A), using an ISOMET Low-Speed Saw (Buehler Ltd., Lake Bluff, Illinois, USA) under water-cooling and then serially polished with BETA-grinder polisher (Buehler, Lake Bluff, Illinois, USA). Thereafter, the specimens were selected based on their surface hardness (SH, 320-380 Knoop) (Fig. 1B) [12].

To induce enamel subsurface lesions, all surfaces of each block were coated with acid-resistant varnish, except the enamel surface. The specimens were immersed in 32 mL of a solution with 1.3 mmol/L calcium nitrate tetrahydrate, 0.78 mmol/L sodium dihydrogen phosphate monohydrate in 0.05 mol/L acetate buffer, pH 5.0; 0.08 mL F, for 16 h at 37 °C (Fig. 1C) [24].

2.4. Synthesis and characterization of nano-sized TMP particles

The process of synthesis and characterization was carried out at the Federal University of São Carlos, based on Danelon et al. (2015) [16], for the study by Emerenciano et al. (2018) [19]. In brief, conventional sodium trimetaphosphate ($Na_3O_9P_3$, Aldrich, purity ≥95 % CAS 7785–84–4) was ball milled using zirconia spheres in 1 L of isopropanol for 48 h. Subsequently, the powders were separated from the alcoholic medium, dried, and ground in a mortar. The resulting powder was characterized by X-ray diffraction (XRD), to identify the structure crystal, as well as to estimate the size of the particles. The milling process did not affect the crystalline structure of TMP. The XRD showed broader peaks due to the smaller crystallites, and the average particle size was 27.7 nm [19].

2.5. Gels formulation and determination of fluoride in the products

All gels were prepared in the Laboratory of Pediatric Dentistry, School of Dentistry, Araçatuba, UNESP (Brazil) and had the following ingredients: carboxymethylcellulose (Sigma-Aldrich Co., St. Louis, MO, USA), sodium saccharin (Sigma-Aldrich Co., St. Louis, MO, USA), glycerol (Sigma-Aldrich Co., St. Louis, MO, USA), peppermint oil (Distriol, São Paulo, Brazil), and water. Sodium fluoride (NaF) was added to the gels at concentrations of 4500 μg F/g and 9000 μg F/g [21]. To the gels containing 4500 μg F/g, TMP was added at 5 %, either as micrometric or nano-sized particles [21]. Furthermore, a gel without F and TMP (Placebo) was prepared as the negative control. To determine the concentration of fluoride in these products, a fluoride ion-specific electrode (9609 BN, Orion, USA) attached to an ion analyzer (Orion, 720 *A*+) was used, and calibrated with standards 0.5-8.0 μg F/mL, as previously described [21]. The mean (SD) pH of gels was 6.5 (0.2), ranging from 6.2 to 6.7.

2.6. Clinical phases of experimental groups

Fluoridated dentifrices (1100 μg F/g as NaF, SorrisoFresh plus gel, Colgate-Palmolive, São Paulo, Brazil) and toothbrushes (Bitufo Class P Extra Soft Toothbrush, Bitufo) were provided to volunteers throughout

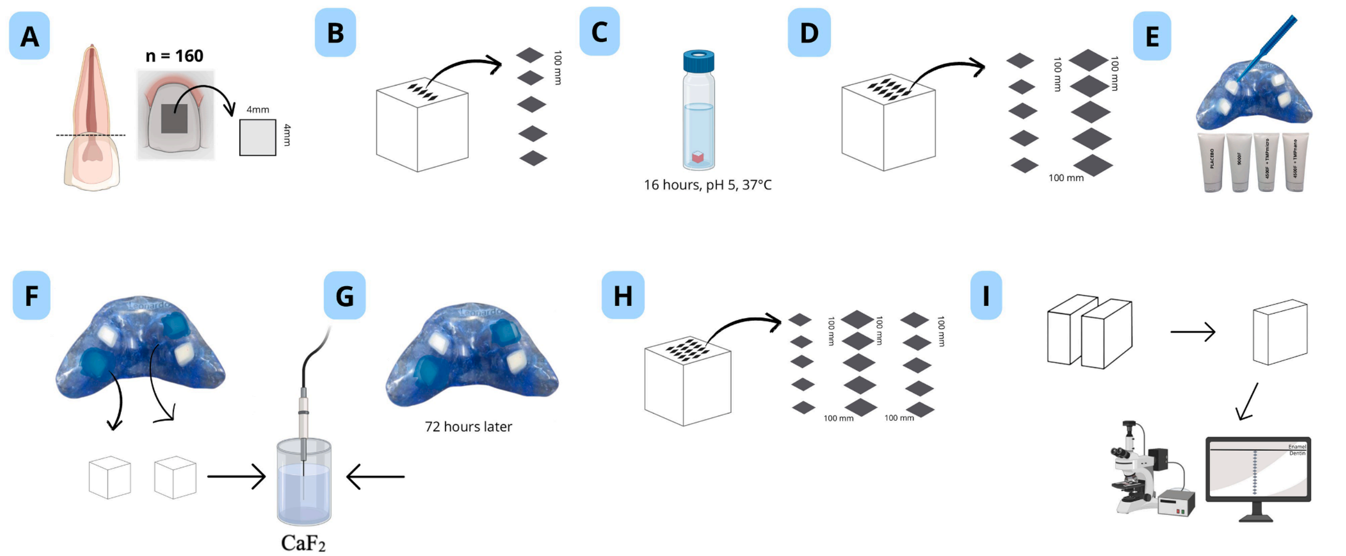

Fig. 1. A representative diagram of the study's experimental design. A. Enamel blocks preparation. B. Surface hardness analysis (baseline). C. Enamel demineralization. D. Surface hardness analysis (post-demineralization). E. Single application of experimental gels. F. Removal of two blocks for analysis of loosely-bound fluoride formed. G. Intra-oral phase and analysis of loosely-bound fluoride retained. H. Surface hardness analysis (final). I. Longitudinal section and subsurface hardness analysis (ΔKHN).

the study [25]. Instructions about the amount of dentifrice (transversal technique) and frequency of brushing (three times/day) were given. These oral hygiene procedures started 7 days before each experimental period [25]. In addition, during the 3-day experimental period, the volunteers were instructed to initially brush their natural teeth to form a natural toothpaste-saliva slurry, followed by three gentle brushing strokes in each enamel block on the palatal appliance [16].

The palatal appliances were inserted in the mouth on the night before each experimental phase to allow the formation of the acquired pellicle [26]. Posteriorly, professional application of topical fluoride was performed on the all-natural teeth of the subjects for each experimental gel [12], following a double-blind, crossover protocol. At the same time, the enamel blocks on palatal appliances were treated for 1 min with the same gels (Fig. 1E). Subsequently, two blocks from each appliance were removed to determine the formation of CaF_2 [12], and the slots were filled with wax (Fig. 1F). At the end of the 3-day experimental phase, the remaining two blocks were removed from the appliance and cleaned to determine CaF_2 retained on the blocks (Fig. 1G), %SHR (Fig. 1H) and ΔKHN (Fig. 1I)[12].

2.7. Analysis of enamel hardness

The enamel microhardness was measured using a Shimadzu hardness tester (HMV-2000, Shimadzu, Kyoto, Japan) with a diamond indenter under a 25 g load for 10 s [27]. Five indentations, separated 100 µm from each other, were made in the center of blocks at the baseline for determining initial surface hardness (SH) (Fig. 1B), and after the induction of subsurface lesions (SH_1) (Fig. 1C). In addition, five other indentations were made (SH_2) spaced 100 µm apart from SH_1 after each experimental phase (Fig. 1H) [27]. The percentage of surface hardness recovery (%SHR) was calculated as $\%SHR= [(SH_2–SH_1)/(SH–SH_1)] \times 100$. For cross-sectional hardness (ΔKHN) analyses, the specimens were longitudinally sectioned, embedded in acrylic resin, and polished. Fourteen indentations, at different distances (5, 10, 15, 20, 25, 30, 40, 50, 70, 90, 110, 130, 220, and 330 µm), were performed in the central area, from the enamel surface, using a Microhardness tester under a 5 g load for 10 s (Buehler, Lake Bluff, USA). The integrated loss of subsurface hardness (ΔKHN; KHN x µm) was calculated using hardness values (KHN), applying the trapezoidal rule [12].

2.8. Analysis of loosely-bound fluoride on enamel

The amount of loosely-bound fluoride (CaF_2-like material) on enamel was quantified immediately after topical application gels (CaF_2 formed), and at the end of each in situ phase (CaF_2 retained). A digital caliper (Mitutoyo CD-15B) was used to measure the surface area of the enamel. Loosely bound fluoride was extracted following the methodology of Caslavska et al. (1975) [28]. A specific-íon electrode (Orion 9609) was used.

2.9. Statistical analysis

SigmaPlot 12.0 software was used for statistical analysis, and the significance level was established at 5%. The data showed normal and homogeneous distributions and were submitted to one-way (%SHR and ΔKHN) or two-way (CaF_2), repeated-measures ANOVA, followed by the Student-Newman-Keuls test.

3. Results

The mean (SD) fluoride concentrations (µg F/g) in the gels were 50.5 (13.0), 9091.2 (284.7), 4131.7 (98.7), and 4387.4 (228.2), respectively for Placebo, 9000F, 4500+5 %TMPmicro and 4500+5 %TMPnano. The mean (SD) of the initial surface hardness of all enamel blocks was 353.4 (8.8). After the induction of subsurface lesions, the mean (SD) percentage of hardness loss was 83.9 (4.51), ranging from 83.5 (4.6) to 84.1 (4.2) without significant differences among the groups ($p = 0.932$).

Significant differences were observed among all groups regarding surface hardness recovery (%SHR), as shown in Table 1. The highest % SHR was observed for the gel containing nano-sized TMP (4500F+5 % TMPnano), followed by 4500F+5 %TMPmicro, 9000F, and Placebo. An inverse pattern was verified for ΔKHN, with the highest and lowest values achieved by the Placebo and 4500F+5 %TMPnano groups, respectively (Table 1).

Regarding loosely bound fluoride (Table 1), significant differences in CaF_2 formed (after topical application) were observed among all groups, with the highest levels observed for the 9000F. A significant decrease was observed for all groups after the 3-day experimental phase. No significant difference was observed among 9000F, 4500F+5 %TMPmicro, and 4500F+5 %TMPnano groups; values for the 4500F+5 %

Table 1
Percentage of surface hardness recovery (%SHR), integrated area of subsurface (ΔKHN), and calcium fluoride concentrations (CaF_2) on enamel, according to the experimental gels.

Groups	Hardness		CaF_2 (μg/cm^2)	
	%SHR	ΔKHN	Formed	Retained
Placebo	14.4 (3.41)^{a}	7105.7 (901.5)^{a}	0.97 (0.57)^{A,a}	0.83 (0.25)^{A,a}
9000F	22.9 (5.05)^{b}	6279.0 (781.5)^{b}	12.44 (3.20)^{A,b}	2.84 (1.43)^{B,b}
4500F+5 % TMPMicro	31.0 (5.50)^{c}	4990.3 (633.3)^{c}	7.29 (2.78)^{A,c}	1.67 (0.81)^{B,b}
4500+5 % TMPNano	40.7 (4.85)^{d}	3972.7 (588.9)^{d}	5.62 (1.86)^{A,d}	1.53(1.27)^{B,ab}

Mean (SD). Different lower case superscript letters indicate significant differences among the gels in each column. Distinct capital letters indicate differences between CaF_2 formed and retained each gel (Student-Newman-Keuls test, $n = 10, p < 0.05$). Placebo = gel without F or TMP; 9000F = 9000 μg F/g; 4500F+ % 5TMPMicro = 4500 μg F/g plus 5 % micrometric TMP; 4500F+5 %TMPNano = 4500 μg F/g plus 5 % nano-sized TMP.

TMPnano group were not significantly different from the Placebo. The Placebo gel promoted the lowest CaF_2 values in both periods.

4. Discussion

The limited action of conventional fluoridated products on the onset and development of dental caries, along with concerns about unwanted side effects, has stimulated the search for actives that act synergistically with fluoride, thus allowing the use of formulations with lower fluoride content without compromising the therapeutic efficacy. The present study demonstrated that gels containing TMP were more effective than a conventional formulation containing twice as much fluoride (9000 μg F/g) in promoting the remineralization of caries-like lesions using an in situ model. In addition, the highest %SHR and the lowest ΔKHN were observed for the gel with nano-sized TMP compared to the formulation containing micrometric TMP. Thus, both null hypotheses were rejected.

Nanotechnology has been widely used in dentistry [29,30], especially for the control of dental caries, aiming at developing formulations that are more effective in enhancing mineral gain and preventing demineralization [31,32]. As previously mentioned, additional effects against enamel de-/re-mineralization and on erosive tooth wear have been attained by the use of TMP nanoparticles when compared to its micrometric counterpart [16,18–20]. Interestingly, an in situ study showed that a conventional (1100 μg F/g) toothpaste containing 3 % nano-sized TMP promoted superior remineralizing effects compared to counterparts without TMP or supplemented with microparticles [16]. It was noteworthy that the toothpaste containing nanoparticles promoted a 43 % reduction in the subsurface lesion (IMR) compared with the conventional formulation [16].

In line with the data above, in the present study, adding 5 % nano-sized TMP to a fluoride gel increased the %SHR by 32 % compared to its micrometric counterpart, supporting the hypothesis of an additional effect of nano-sized TMP. These results can be explained by some physicochemical properties of nanoparticles, which make the nano-sized TMP more reactive than micrometric TMP [16,29]. Nanoparticles, by convention, are smaller than 100 nm and present a high ratio of surface area to volume. The lower size of the nanoparticles (compared with micrometric ones) results in marked changes in the atomic arrangement within the nanoparticle, with their atoms located at the surface or a few atomic distances from the surface. This confers a large chemical potential, resulting in a high atomic diffusion and reactivity [29,33]. Another parameter that shows the benefit of the gel containing TMPNano is the ΔKHN value, which was 25 % lower than the gel with phosphate at the micrometric scale. It is plausible to assume that the superior remineralizing effect of the gel containing nanosized TMP is related to its action on the lesion body. This is consistent with the findings of Danelon et al. (2015) [16], who reported that the capacity to reduce the lesion body (IMR) was 22 % greater when using a dentifrice containing 1100 μg F/g combined with nanosized TMP, compared to its micrometric counterpart. This is extremely desirable from a clinical standpoint, as it may suggest a higher degree of lesion recovery in contrast to what is usually observed for conventional fluoridated formulations (i.e., hypermineralization of enamel surface with lesser effects on the subsurface).

Regarding loosely bound fluoride (CaF_2), a dose-response relationship between fluoride content in the products and CaF_2 formed on the enamel was observed, consistent with the existing literature [5]. Nonetheless, despite the 9000 μg F/g gel promoting the highest CaF_2 concentration, the resulting %SHR values were lower than those related to the TMP-containing formulations. This pattern was also observed for TMP-containing varnishes, whose remineralizing effects have been associated with lower deposition of CaF_2 and F [25,34], which may be unexpected, at first glance, when considering the existing knowledge on the mechanisms of action of fluoride on caries control [5]. Given the similar trends observed for TMP-containing varnishes [25,34] and gels (present study), these data analyzed together reinforce the concept that different mechanisms are related to the effects of TMP on caries dynamics. The mechanism of action of TMP has been related to its capacity to adsorb to enamel and retain calcium and fluoride ions [14], which are released upon acidic pH [34]. As TMP and F compete for the same binding sites on the enamel surface, higher fluoride concentrations can interfere with TMP action [17], which justifies the need to determine an ideal TMP:F molar ratio to achieve maximum synergistic effects [11].

The discrepancies between the current results and the in vitro data reported by Nagata et al. (2023) [21] on enamel remineralization, also using TMP-containing gels, should be further addressed, and are likely to have resulted from the different protocols employed. While in the in vitro protocol the remineralization process was produced by static immersion in solutions and a single topical fluoride application was performed, the present in situ study included interactions between enamel and salivary ions, the presence of the acquired enamel pellicle, and salivary buffers, bringing it closer to reality. Furthermore, in the present in situ study, the volunteers brushed their teeth with fluoridated toothpaste three times daily, which provided an additional F source to interact with enamel (coated by a TMP layer). Another reason for the differences observed might be the duration of the experimental periods, respectively 3 and 7 days for in situ and in vitro protocols [35].

Despite the promising results, this study has some limitations. First, the short duration of the in situ protocol (3 days) may not fully replicate long-term clinical conditions or the dynamics of caries lesion progression [36]. Second, the absence of biofilm accumulation and cariogenic challenges (e.g., sucrose exposure) limits the extrapolation of the findings to high-risk clinical scenarios [2,37]. Moreover, the processes of demineralization and remineralization in vivo, and consequently of dental caries, are influenced by a complex interplay of factors, including individual variations in salivary flow and composition, diet, frequency of sugar intake, oral hygiene habits, and the microbiological profile of the dental biofilm [37,38]; none of which were reproduced in the present model. Additionally, the present study uses bovine enamel as a substrate, which, despite being an accepted substitute for human enamel in in vitro and in situ studies, presents important physicochemical differences [39,40]. Bovine enamel is generally more porous and less mineralized than human enamel, which may facilitate greater ion diffusion and, consequently, enhance the rate and extent of remineralization observed [40]. Lastly, the artificial caries lesions created in this study were relatively shallow [24], which likely contributed to the more pronounced remineralizing effects of the tested formulations [40]. Therefore, caution is needed when extrapolating these findings to deeper or more clinically advanced caries lesions in human teeth.

In summary, the present study demonstrated that the addition of nano-sized TMP to fluoridated gel led to the highest remineralization rate of artificial caries lesions under in situ conditions, surpassing that achieved by the use of a conventional formulation containing twice as much fluoride. Considering these results, the low-fluoride gel with TMPnano could be a safe and promising alternative in clinical practice, since it has a higher remineralizing capacity and offers a lower risk of acute side-effects compared with a conventional formulation. Clinical trials are needed to confirm the effects of nano-sized TMP.

5. Conclusion

Based on the data obtained and considering the limitations of the experimental model, it can be concluded that using low-fluoride gels containing TMP, in combination with fluoridated toothpaste, resulted in significantly greater remineralization compared to a conventional gel with twice the fluoride concentration. Moreover, nano-sized TMP particles promoted more effective remineralization than their micrometric counterparts, thus being a promising strategy for clinical caries management.

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CRediT authorship contribution statement

Tamires Passadori Martins: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Liliana Carolina Báez-Quintero:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Isabela Maria Passarela Gomes:** Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Annette Wiegand:** Writing – review & editing, Formal analysis. **Alberto Carlos Botazzo Delbem:** Writing – original draft, Visualization, Supervision, Resources, Project administration, Funding acquisition. **Juliano Pelim Pessan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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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