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ORIGINAL ARTICLE

Nanoencapsulated fluoride as a remineralization option for dental erosion: an *in vitro* study

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ABSTRACT

Objective: To compare the *in vitro* performance of different dentifrices indicated for dental erosion and a new dentifrice with controlled fluoride release system (NanoF) in terms of surface microhardness remineralization in enamel erosion lesions.

Materials and methods: 72 human enamel specimens were divided into 6 groups ($n = 12$): PC (100% NaF – positive control); NC (Placebo – negative control); 50%nF (50% NanoF + 50% free NaF), 100%nF (100% NanoF); PN (Sensodyne® ProNamel™) and AG (Colgate® Sensitive Pro-Relief™). A surface microhardness analysis was performed before (SH_0) and after (SH_1) the erosion lesion formation. The blocks were submitted to a 5-day de-remineralization cycling model, consisting of 90 s immersion on 0.1% citric acid (4x/day) and 1 min treatment with dentifrice slurries along with 1 mL/block of human saliva (2x/day). Lastly, the final surface microhardness analysis (SH_2) was measured and the percentage of surface microhardness remineralization ($\%SMH_R$) was calculated. Data were analysed with 2-way ANOVA and Tukey's test ($p < .05$).

Results: Statistically significant differences were observed for SH_2 and $\%SMH_R$ between NC and AG with the other groups ($p < .05$). The best $\%SMH_R$ from the experimental groups was found in 100%nF and PN.

Conclusion: Dentifrices with NanoF exhibited a surface microhardness remineralization similar to sodium fluoride (PC). Therefore, NanoF dentifrice can be an alternative to prevent and treat patients with dental erosion.

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Introduction

Dental erosion has become increasingly prevalent in the population throughout the world [1,2]. It is a clinical condition resulting from a chemical process of recurrent exposure to acidic substances without bacterial involvement, which cause the enamel softening with losses of mechanical resistance and structural integrity [3,4]. Over the decades, the increased intake of acidic foods and beverages [5,6] has led the scientific community to search for novel products and compounds that can act in the prevention as well as in the remineralization of eroded enamel [7–10].

Strategies for addressing dental erosion involves the control of risk factors and the use of preventive measures [11,12]. In this context, *in vitro* studies have demonstrated the remineralizing potential of dentifrices with potassium nitrate (KNO_3) [4,13,14], claiming to protect the tooth against dental erosion by presenting in its formulation a high concentration of available fluoride, reducing demineralization and increasing the hardness of the enamel surface after an erosive attack [4]. Arginine, in turn, when added to dentifrices, has complementary actions with calcium carbonate and fluoride, promoting mineral deposition on the exposed surface [15].

Fluoride and saliva are regarded as the most important factors for repairing softened enamel [16]. Fluoride is known for its ability to enhance remineralization and greatly reduce demineralization under mild acidic environments (e.g.: the cariogenic challenges in the oral cavity) [17]. Therefore, the effective prevention of dental erosion requires the use of products with technologies that enable greater substantivity of the fluoride ion and that are stable enough to maintain the barrier against erosive challenges [10].

Researchers have provided considerable attention to the drug delivery systems (DDS), as devices that can transport and release therapeutic agents or bioactive substances in the buccal cavity [18]. Nanotechnology has been gaining prominence in preventive and therapeutic dentistry as a slow-release system for substances that can control and treat buccal problems [19–23]. Nanoencapsulated fluoride (NanoF) acts as a controlled release system. It has a double molecular

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polymer (natural biopolymer of hydroxypropyl guar) as the drug carrier, requiring activation by a salivary enzymatic trigger (amylase) to be released, maintaining a therapeutic concentration of fluoride in the buccal cavity for an extended period.

Therefore, this *in vitro* study aimed to verify the performance of fluoride dentifrices in the remineralization of erosive lesions using nanoencapsulated fluoride (NanoF), 5% potassium nitrate (KNO_3) and arginine. The null hypothesis was that NanoF, potassium nitrate 5% and arginine dentifrices associated with fluoride have no ability to remineralize eroded dental enamel as conventional NaF.

Materials and methods

Ethical consideration

Considering the use of human teeth, a Research Ethics Committee in Brazil approved this study (CAAE: 59409816.9.0000.5188). All the donated teeth were collected from the Human Teeth Bank of the Federal University of Paraiba. The teeth donors were explained about the aims and relevance of this research and signed the Informed Consent Form according to the Helsinki Declaration and the Brazilian resolution (CNS/MS 466/12).

Experimental design

Enamel specimens ($4 \times 4 \times 2$mm) were prepared from a mid-buccal and/or lingual surfaces of extracted caries-free human third molars, and stored in 0.08% thymol solution. The specimens were embedded in self-cured acrylic resin, using circular moulds (16 mm × 3 mm). The outer enamel surface was ground flat with grit papers (600–1500 grades) underwater refrigeration and polished with 1 μm diamond paste (Extec Corporation, Enfield, CT) in a rotating polishing Machine PSK-2V (Skill-tec Comércio e Manutenção Ltda, São Paulo, SP, Brazil).

Sample size

Sample size was measured for the primary outcome of this study (surface microhardness remineralization). Based on a previous study [24] and considering a two-sided alpha of 0.01 and a power of 80%, this study requires 6 samples per group. A total of 72 enamel specimens were randomly distributed into six groups ($n = 12$), according to their surface microhardness: PC (dentifrice with 100% NaF fluoride); NC (dentifrice without fluoride); 50%nF (dentifrice with 50% NanoF + 50% NaF free); 100%nF (dentifrice with 100% NanoF); PN (dentifrice with Potassium Nitrate 5%) and AG (dentifrice with Arginine), coded by an independent researcher, as described on Box 1.

The enamel surface of each specimen was divided into three equal parts and one was recovered with a double layer of nail polish (Risqué Tecnologia, COSMED Indústria de Cosméticos e Medicamentos S/A, São Paulo, Brazil), to preserve a control area of each specimen.

Firstly, baseline enamel surface microhardness (SH_0) analysis was performed with a microhardness tester (Shimadzu HMV – AD Easy Test Version 3.0). Five indentations spaced 100 μm from each other were made at the centre of the enamel surface (Vickers, 100 g, 10 s). Then, an erosion lesion (SH_1) and treatment (SH_2) were performed on the remaining two parts.

Erosion lesion formation

An initial enamel erosion lesion was carried out using a model according to Comar et al. [25]. Following 5 min sonication in water using an ultrasonic device, the enamel blocks were immersed individually in 0.1% citric acid (pH 2.5) for 30 min, at room temperature (28°), under gentle horizontal agitation (60 rpm). The acid solution was replaced every 5 min (30 mL/sample). After acid exposure, the blocks were submitted to a post-demineralization surface microhardness (SH_1) with the same parameters described previously. The percentage of surface microhardness change was calculated ($\%SMH_C = (SH_0–SH_1)/SH_0 \times 100$) to randomize the enamel blocks in the treatment groups.

Collection of human saliva

It was recruited 12 individuals between 18 and 35 years old, both gender, without system involvement and resident in a city without fluoridated water. Subjects who used drugs that interfere in the salivary flow or who used fluoride products in the last four weeks; who used orthodontic appliances; presence of caries and/or erosion lesions and/or periodontal disease, were excluded from the sample. Stimulated human saliva was collected each day of the study. Each volunteer chewed paraffin wax and expectorated the stimulated saliva

Box 1. Dentifrices used in the study according to their composition and manufacturer*.

Group	Composition	Manufacturer
PC (Positive control – 100% NaF)	100% sodium fluoride – NaF (1450 ppm fluoride)	SAVOY, Jundiaí, São Paulo, Brazil
NC (Negative control – no fluoride)	No fluoride	SAVOY, Jundiaí, São Paulo, Brazil
50%nF (50% Nano*F* + 50% NaF free)	50% Nano*F* + 50% NaF (1450 ppm fluoride)	SAVOY, Jundiaí, São Paulo, Brazil
100%nF (100% NanoF)	100% NanoF (1450 ppm fluoride)	SAVOY, Jundiaí, São Paulo, Brazil
PN (Sensodyne ProNamel®)	Potassium nitrate 5% (1425 ppm of NaF)	GlaxoSmithKline Brazil Ltda, Jacarepaguá, Rio de Janeiro, Brazil
AG (Colgate® Sensitive Pro-Relief™)	8% Arginine + 1.1% Sodium Monofluorophosphate (1450 ppm fluoride)	Colgate-Palmolive Company, Rio de Janeiro, Rio de Janeiro, Brazil

*All experimental dentifrices included the following ingredients: water, carboxymethyl cellulose (binder), sodium lauryl sulphate (surfactant), hydrated silica (abrasive), 70% sorbitol and glycerine (humectants), and methylparaben (preservative).

into a plastic cup, as performed by Eversole et al. [26], and stored in the refrigerator at 5 °C until use.

Remineralizing pH-cycling

Before the remineralization pH cycling model, the enamel specimens had another one third of their surface covered with two layers of nail varnish (Risque, Niasi, Taboão da Serra, São Paulo, Brazil) as a reference for erosion lesion area. The specimens were individually submitted to a pH cycling model at 37 °C during 5 days [25]. The erosive challenge was performed by immersion in 0.1% citric acid (pH 2.5) solution, for 90 s, 4 times a day. After each demineralization, the specimens were rinsed with deionized water (10 s) and subjected to treatment with the respective dentifrice slurries (dentifrice:deionized water, 1:3 w/w; 2 mL/enamel specimen) for 1 min, under agitation. During the treatment, all groups had an addition of 10% of its volume of human saliva, for salivary amylase activation on NanoF groups. Following each treatment, the specimens were transferred into a remineralization solution (pH 6.8, 30 mL/specimen, unstirred, 25 °C) for 2 h. After the last daily erosive treatment, the specimens were also stored in a remineralization solution overnight. The citric acid was renewed at each erosive challenge, and the remineralization solution was replaced daily. The remineralization solution consisted of 1.5 mM.L^{-1} calcium, 0.9 mM.L^{-1} phosphate, 150 mM.L^{-1} potassium chloride in 0.02 mM.L^{-1} cacodylic buffer, pH 7.0; 0.02 μgF/mL, 1 mL/mm^2. Deionized water rinses were performed between each step.

After the remineralizing pH-cycling and treatments, the nail varnish was removed and enamel surface microhardness was again determined (SH_2) as baseline profile parameters. The values were averaged (μm) and the percentage surface microhardness remineralization was calculated as following formula:

$$\%SMH_R = (SH_2 - SH_1)/(SH_0 - SH_1) \times 100.$$

Statistical analysis

Data were statistically analysed using the SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA). Normal Distribution and homogeneity of variances were tested using the Shapiro-Wilk test and Levine test, respectively. Since data demonstrated homogeneity of variances and Gaussian distribution, no data transformation was needed. Assumptions of analysis of variance were checked before the use of two-way factorial analysis of variance (ANOVA) model to investigate surface microhardness remineralization into different groups among the dependent variable ($\%SMH_R$), and ANOVA Repeated Measures, followed by Bonferroni, for the analysis of the variables SH_0, SH_1, SH_2 into the same group at the different analysis times. The level of significance considered was 5% ($p < .05$).

Results

The average values of surface microhardness and standard deviation for the variables SH_0, SH_1 and SH_2 are described in Table 1. For SH_0, the average of surface microhardness ranged from 411.25 to 432.41 and for SH_1 there was a range from 231.81 to 254.53. For the variable SH_2, the highest mean found was 348.02 (group 100%nF) and the lowest 257.35 (group AG). Comparing each group individually, there was a statistically significant difference between the times SH_0 and SH_1 and between SH_1 and SH_2, for all groups ($p < .05$), except for the Colgate Sensitive Pro-Relief ™ (AG), which did not undergo remineralization after treatment.

When comparing the groups by the variables SH_0, SH_1 and $\%SMH_C$, no significant differences were observed between the groups ($p > .05$). However, for SH_2 (ANOVA, $p < .05$), there were statistically significant differences between them ($p < .05$). It is noticed that the AG showed similar behaviour to the placebo (NC) ($p > .05$), while the 50%nF, 100%nF and PN groups were similar to the PC ($p > .05$).

Graph 1 shows the averages of the $\%SMH_R$ values for all groups analysed. Statistically significant differences were observed between the groups ($p < .05$), following the same pattern observed for the variable SH_2. AG (4.15) had the lowest $\%SMH_R$ among all groups analysed, while the PC had the highest (30.77) (Figure 1).

Table 1. Mean and standard deviation of enamel surface microhardness values, performed at different times of analysis.

Groups/Dentifrices	SH_0 (sd)	SH_1 (sd)	SH_2 (sd)	F-value, *p*-value*
PC Positive Control (100%NaF)	^{a}421.59(26.72)^{A}	^{b}231.81(33.35)^{A}	^{c}336.15(30.04)^{A}	152.17, 0.000
NC Negative Control	^{a}411.25(16.07)^{A}	^{b}232.84(30.59)^{A}	^{c}264.38(41.75)^{B}	152.18, 0.000
50%nF 50%Nano*F* + 50%NaF	^{a}415.30(37.68)^{A}	^{b}232.97(42.59)^{A}	^{c}310.19(38.11)^{A}	71.40, 0.000
100%nF 100%NanoF	^{a}432.51(27.26)^{A}	^{b}254.53(23.21)^{A}	^{c}348.02(46.88)^{A}	79.55, 0.000
PN Sensodyne ProNamel®	^{a}424.95(24.20)^{A}	^{b}237.04(38.01)^{A}	^{c}332.59(40.26)^{A}	115.89, 0.000
AG Colgate® Sensitive Pro-Relief™	^{a}424.25(41.42)^{A}	^{b}242.69(28.00)^{A}	^{b}257.35(36.82)^{B}	142.87, 0.000

*Means preceded by distinct lower case letters differ statistically within the same line for each group, $p < 0.05$, ANOVA Repeated Measures, followed by the Bonferroni test.
**Different capital letters differ statistically between groups for each variable, in the same column, $p < .05$, ANOVA (SH_0: $F = 0.82$, $p = .534$; SH_1: $F = 0.895$, $p = .489$; SH_2: $F = 12.262$, $p = .00$) followed by the Tukey test.

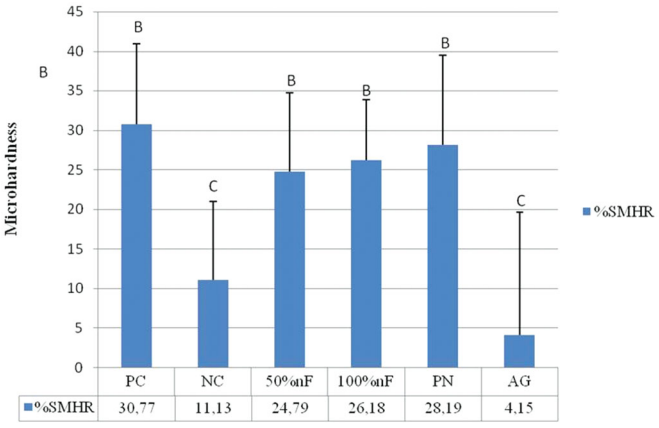

Figure 1. Averages of $\%SMH_R$ values between the analysed groups*. *Different capital letters represent significant differences between groups, for each variable analysed (ANOVA, $p < .05$).

Discussion

Novel options for drug delivery systems have been explored to find effective formulations and components that might boost the beneficial effect of fluoride dentifrices [27], preventing dental erosion and remineralizing eroded enamel [7–10,13,28]. NanoF emerged as an innovative, unprecedented method for increasing the substantivity and bioavailability of fluoride ions in the buccal cavity. We evaluated a controlled release system with NanoF that delivers fluoride ions more slowly, using an *in vitro* pH cycling model. For this, it was also used a well-established positive control in the literature as effective for the remineralization of eroded enamel [9,10,28].

Dentifrices with 50% NanoF and 100% NanoF demonstrated a satisfactory surface microhardness remineralization. The absence of statistically significant difference between these groups and the PC and PN groups indicates that these products have effective remineralizing potential. The composition of the NanoF is basically sodium fluoride (NaF) encapsulated in a natural biopolymer (hydroxypropyl guar). The guar gum is a molecular weight carbohydrate polymer which is derived from the natural seed of the guar plant (*Cyamopsistetragonoloba*(L.) Taub). The particle size is about 200 nm. The fluoride release is not dependent on pH but on enzymatic triggers following a mechanism of stimuli-controlled release. In the buccal mouth, a previous clinical study [29] showed that the fluoride release in saliva is delayed within the first 60 min after brushing. Moreover, the incorporation of fluoride ions in the dental biofilm was also prolonged when compared to regular NaF dentifrices (data not shown).

The system of nanoparticles covered with a bioadhesive polymer of low molecular weight allows a controlled release of fluoride by biodegradation of this polymer through the action of salivary amylase [30]. The nanoscaled size of the particle released ensures unique properties of high surface to volume ratio, ability to penetrate the biofilm and, thus, a higher concentration of this ion on the enamel surface [30,31].

The NanoF used in this study was a controlled release system. The treatment time of only one minute may have affected its performance, since increasing this variable may further improve the enzyme's performance and the action of NanoF. This may be a hypothesis based on the good performance of the NanoF dentifrices when compared to the PC on this pH cycling model. Also, this aforementioned hypothesis, can be based on the results of a clinical and *ex vivo* studies involving the same experimental dentifrice, in which Moreira [29] found that dentifrices with NanoF led to higher salivary concentrations of fluoride over time, compared to dentifrices with free NaF and a placebo. In the same study, 100% NanoF led to the highest levels in saliva even one hour after the use of fluoride dentifrices [29]. Thus, longer treatment times enable greater bioavailability, which is described as necessary in the mechanism of action of fluoride for the treatment of enamel erosion [10,32].

The availability of fluoride in dentifrices is considered an important factor to its protective and/or remineralizing potential [27]. In this study, for comparative purposes, without using nanotechnology, we used fluoridated dentifrices containing potassium nitrate (PN) and arginine (AG), which are indicated for the treatment of erosive lesions by the manufacturers. PN dentifrice was developed to limit potential interactions with excipients and, therefore, provide high levels of bioavailable fluoride [28]. The surface microhardness remineralization found for PN in this investigation is in accordance with the findings described by Zawaideh et al. [4], Fita & Kaczmarek [13], Lacerda [14] and Zanatta et al. [33]. In contrast, Kato et al. [34] and Faller et al. [35] reported that this product had the greatest surface loss.

Dentifrices incorporate arginine in its formulation to act in conjunction with calcium carbonate and fluoride to promote mineral deposition on the exposed surface [36]. Conflicting findings are described in the literature regarding the performance of these components in remineralization/protection of dental erosion [14,28,33–36]. A poor performance was also found in other studies [14,28,35,37], demonstrating that this product acted as a placebo or dentifrice without fluoride. In contrast, Rege et al. [15], Yamashita et al. [38] and Sullivan et al. [39] found a satisfactory remineralizing potential. A layer rich in calcium was observed on the demineralized enamel, in which arginine is believed to modify the enamel surface charge, increasing the affinity of calcium carbonate for the dental surface and filling the microscopic spaces created by the acid, which would lead to enamel recovery and protection of the surface against future erosion challenges [15]. However, this may not guarantee the effective remineralizing action of the toothpaste, since, according to Lussi et al. [10], the calcium carbonate layer is very soluble and has a short life to lead to precipitation of the mineral, which may explain its lack of remineralization performance in the model used. Also, AG has sodium monofluorophosphate in its composition, which needs to be cleaved in the oral environment through phosphatases to release ionic fluoride and act in the remineralization process. Finally, discreet surface microhardness remineralization was presented in the NC group that may have been due to the type of model used, remineralizing, which is characterized by a remineralization > demineralization [40].

However, this study used an *in vitro* methodology that has some limitations: (1) the impossibility to simulate all variables of the buccal environment; (2) substrate conditions and saliva used are limited; (3) demineralization-remineralization processes occur quickly, leading to a lower clinical relevance than *in situ* analyses. Nevertheless, we added 10% human saliva to the dentifrice slurries tested, during pH cycling, for salivary amylase activation on NanoF groups and to simulate, in a way, the buccal conditions. Despite the *in vitro* study limitations, dentifrices containing sodium monofluorophosphate are routinely tested using this model [14,28,35,37,41,42] and pH cycling is considered an effective alternative for simulating the oral environment [40].

In vitro studies have contributed to understanding the compatibility of new ingredients with fluoride and testing the efficacy of new remineralizing formulations [43]. Laboratory methods provide highly controlled and cost-effective conditions, attempting to mimic clinical conditions [44]. The absorption of fluoride by enamel is believed not to be merely a function of the free availability of this compound but rather depends on the formulation of the dentifrice used [27]. Controlled drug release systems have been the object of numerous scientific studies. It is also possible to enhance the properties of certain materials by encapsulation in a polymeric film [45]. The surface microhardness remineralization of dentifrices with NanoF fluoride in a controlled release system underscore the importance of fluoridated dentifrices for the remineralization of eroded enamel. Thus, further research, clinical trials and *in situ* studies, should be conducted to confirm the present findings.

Conclusion

The NanoF and potassium nitrate dentifrices provided a surface hardness remineralization in the erosive lesions similar to that found for the positive control. Therefore, NanoF dentifrice can be an alternative to prevent and treat patients with dental erosion.

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