RESEARCH PAPER

Effect of Marine Shell-Derived Nano-Hydroxyapatite Incorporated into Fluoride-Containing Arabic Gum on Enamel Remineralization: An In Vitro Study

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ABSTRACT

Introduction: Dental caries is a dynamic process involving recurrent demineralization and remineralization at the tooth–biofilm interface. Arabic gum promotes remineralization through its high calcium ion content, facilitating the replacement of calcium ions in demineralized enamel. Similarly, nano-hydroxyapatite, due to its biomimetic similarity to enamel apatite, enhances remineralization by integrating into the enamel structure and promoting crystal growth. Aim: This in-vitro study aimed to evaluate the remineralization of demineralized enamel using Arabic Gum and fluoride ions added to Nano-hydroxyapatite synthesized from biogenic marine shells, compared with MI Paste Plus. Materials and Methods: Sixteen human premolar teeth were coated with nail varnish except for the buccal surface. Artificial carious lesions were induced using a demineralizing solution. Then, the samples were randomly divided into two groups (n=8) based on the material used: Group A, Arabic Gum + F- + Nano-HAp; and Group B, MI Paste Plus. Each group underwent pH cycling for 14 days. Surface topography (SEM) and mineral content (EDX) were analyzed at baseline, after demineralization, and after pH cycling. Results: The remineralizing Ca/P values were significantly higher than the demineralizing values in both groups. Regarding the Ca/P ratio during the remineralizing phase, there was no significant difference between group A (1.82±0.03) and group B (1.76±0.03). Conclusion: Nano-HAp derived from marine waste demonstrated a remineralizing ability when combined with Arabic Gum and fluoride ions.

Keywords: *Arabic gum, Fluoride ions, Marine shells, Nano- HAp, Remineralization*

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INTRODUCTION

The remineralization process is a natural repair mechanism that restores minerals, in ionic form, to the hydroxyapatite (HAp) crystal lattice. (1) In a normal oral environment, hydroxyapatite on the enamel surface contacts saliva, maintaining the balance of dissolution and redeposition. (2,3) Hydroxyapatite dissolves into calcium and phosphorus ions, which can then crystallize in a controlled, organized fashion from saliva, forming an enamel-like hydroxyapatite layer on the enamel surface. (4)

Nano-HAp has gained significant attention in recent years for its role in various preventive, therapeutic, and regenerative applications. Since it is the main component of bone and teeth and is biocompatible, hydroxyapatite has become one of the most extensively studied biomaterials in the medical field. (5,6)

Tooth preservation and overall oral health depend on remineralization. Nano-HAp has demonstrated a remineralizing effect on artificial carious lesions and has been shown to build a new enamel layer. (7,8) Due to its remineralizing ability on enamel, some experts believe it is a bionic material capable of regenerating enamel. (9)

Arabic Gum is derived from the stems and branches of various African Acacia species. It contains high-molecular-weight polysaccharides and is rich in minerals like calcium, magnesium, and potassium salts, which, when hydrolyzed, produce arabinose, galactose, rhamnose, and glucuronic acid. (10) Arabic Gum inhibits acid-driven demineralization and encourages remineralization even without fluoride present. (11)

No published research has explored the remineralizing effect of adding Nano-HAp to Arabic Gum and fluoride ions. Therefore, this in vitro study was conducted to evaluate the impact of adding Nano-HAp to Arabic gum

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and fluoride ions on tooth remineralization, and to compare it with MI Paste Plus.

MATERIALS AND METHODS

Materials:

Table 1: Name and Manufacturer of materials used in this study

Material Name	Manufacturer
Nano-HAp	Synthesized from Biogenic marine shells by the chemical precipitation method at the Laboratory of Inorganic Chemistry, Faculty of Science, Suez Canal University by **Prof. Dr. Sabry Abd El Hamid El-Korashy**.
Arabic Gum	Suzhou, Jiangsu, China
Fluoride ions (Sodium Fluoride powder)	BDH chemicals, Poole, England
MI Paste Plus	GC AMERICA INC, USA

METHODS

Preparation of experimental HAp nano-powder from marine shells:

Hydroxyapatite was prepared from marine shells using the CaO phase. It was achieved by calcining cleaned and dried marine shells at 950 °C for 2 hrs. CaO was dissolved in 2 molar HNO_3 before being diluted with deionized water to produce a 0.1 M. Ca $(NO_3)_2$ solution. 0.06 M. of $(NH_4)_2HPO_4$ solution was slowly added to finally obtain a Ca/P ratio of 1.67. The pH of the mixture was adjusted to 10 by adding 1 M. NH_4OH solution. The white milky precipitate obtained was centrifuged and filtered. It was washed several times with deionized water before being dried in a drying oven at 80°C for 12 hrs. Finally, Nano-HAp solids were obtained by calcination at 700 °C for 2 hrs. Afterwards, the calcined powder was finely ground in a Zirconia ball-mill and sieved to a particle size below 30 µm before characterization. (12)

2. **Characterization of the prepared powders using various analytical techniques:**

a) Transmission Electron Microscope (TEM)

The crystal size of Nano-HAp powder was measured using high-resolution TEM (JEM-HR-2100, Japan) at an accelerating voltage of 200 kV.

b) Fourier Transform Infrared spectroscopy (FTIR):

An Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) Spectrometer (Bruker, Germany, Alpha-P) was used to generate direct information about the sample's molecules.

c) Energy Dispersive X-ray analysis (EDXA):

Elemental analysis of Nano-HAp was performed using an EDX unit with an accelerating voltage of 20 kV.

Teeth collection and sample preparation (Stage 1):

Sixteen sound, non-carious human premolars freshly extracted for orthodontic purposes were collected from the clinic of Maxillofacial Surgery, Faculty of Dentistry, Suez Canal University. The purpose of the present study was explained to the patient, and informed consent was obtained to use the patient's extracted teeth in the research, in accordance with the guidelines on human research published by the Research Ethics Committee at the Faculty of Dentistry, Suez Canal University. Teeth with restorations, enamel cracks, caries, erosion, developmental defects, or white spot lesions were excluded. (13)

Calculus and remaining soft tissue were removed manually using a scaler and a periodontal curette (Carl Martin GmbH, Solingen, Germany). Afterwards, they were polished with fluoride-free pumice paste. Finally, the teeth were rinsed with distilled water and then stored in normal saline until further use. (14)

All the tooth surfaces were coated with two successive layers of acid-resistant nail varnish (Amanda Long Lasting, Milano, Italy), except for the buccal surface. (15)

Caries induction (Stage 2):

Each tooth was individually and vertically suspended from the root by a string in 20 ml of demineralizing solution with pH = 4.4 (2.2 mM $CaCl_2$, 2.2 mM $NaHPO_4$, 50 mM CH_3COOH). Teeth were stored at 37°C for 96 hours. The solutions were replaced, and the teeth were rinsed with distilled water every 12 hours. After demineralization, a white opaque layer was observed on the entire surface of each treated tooth. An acid etchant consisting of 35% phosphoric acid solution (Ultradent Products Inc., USA) was applied to the white opaque layer on each tooth for 30 seconds. This was followed by rinsing with distilled water and air drying. This process effectively removed the white opaque layer and revealed the underlying artificial caries. (16,17)

pH-cycling (Stage 3):

A remineralizing solution containing 1% Nano-HAp, 500 ppm fluoride ions, and 10 mg/ml Arabic Gum was prepared for use as a group intervention in pH cycling. The teeth were randomly divided into two groups (n=8) based on the remineralizing agent used. Each tooth underwent the specified pH-cycling regimen to mimic real-life intraoral conditions. (18) This regimen was carried out over 14 consecutive days (Table 2).

Each tooth was individually and vertically suspended from its root by a string in its specific solution, following the scheduled cycle, and placed in an incubator at 37 °C. Each tooth was rinsed with distilled water for 1 minute before being moved to the next test tube. All solutions were refreshed every 48 hours. For MI Paste Plus, the paste was applied with a fine micro applicator (TPC Disposable Micro Applicators, Inc. 18525 E., USA) to fully cover exposed enamel. The paste was left untouched for five minutes, according to the manufacturer's instructions. Each tooth was then suspended in 20 ml of fresh artificial saliva (pH=7) (1.5 m M $CaCl_2$, 90 m M KH_2PO_4, 50 m M KCl, 2.42 gm Tris buffer) at 37 °C for 7 hours.

Table 2: Daily pH cycling schedule for demineralized teeth over 24 hours.

Type of treatment	Time of application	
Demineralizing solution	1 p.m	1:30 p.m
Artificial saliva	1:30 p.m	6:30 p.m
Demineralizing solution	6:30 p.m	7 p.m
Artificial saliva	7 p.m	12 a.m
Demineralizing solution	12 a.m	12:30 a.m
Artificial saliva	12:30 a.m	5:30 a.m
Demineralizing solution	5:30 a.m	6 a.m
Groups intervention	6 a.m	1 p.m

Microstructural characterization and Elemental analysis:

The enamel surfaces were examined using SEM (Quanta 250 FEG). Images were captured at magnifications of 2000x, 5000x, and 8000x. Scanning was conducted in three different stages: Stage 1, Stage 2, and Stage 3. The surface mineral content (atomic percentage) was measured using EDX analysis (Quanta 250 FEG) at a magnification of 5000x.

Statistical analysis:

Numerical data were presented as mean ± SD values. Data normality and homogeneity of variance were checked using the Shapiro-Wilk and Levene's tests, respectively. All assumptions were confirmed, so two-way mixed Aligned Rank Transform (ART) models were employed for analysis. Post hoc comparisons of estimated marginal means used the main model's error term, with p-values adjusted for multiple comparisons via Holm's method. Significance was set at $p<0.05$.

RESULTS

Characterization of Nano- HAp:

1. TEM of the Nano-powders:

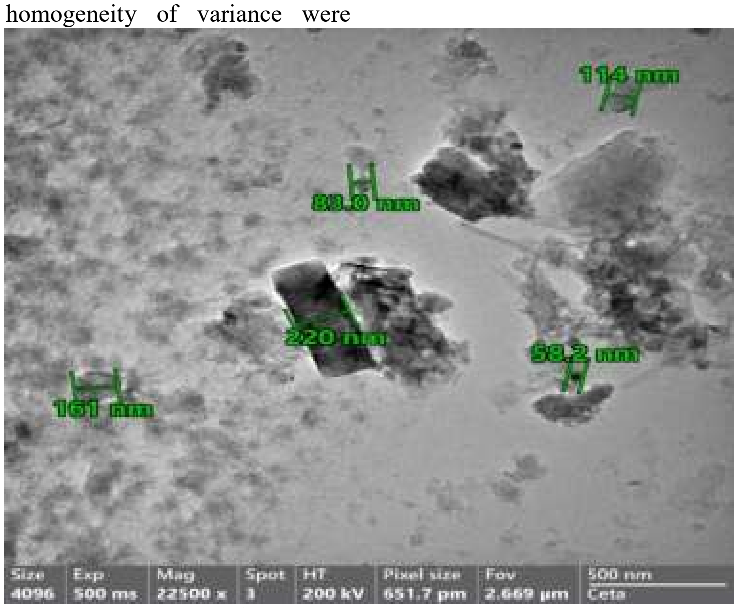

Figure 1: TEM of Nano-HAp (average crystal size= 127nm).

2. FTIR characterization for Nano-HAp powders:

The IR spectra of the Nano-HAp powder showed typical absorption bands related to the bending vibration modes of O-P-O bonds in the phosphate group $(PO_4)^{3-}$ at: 462 cm-1, 565 cm-1and 601 cm-1. Moreover, the asymmetric stretching vibration P-O bonds in the phosphate group appeared at 1021 cm-1 (Figure 2 and Table 3).

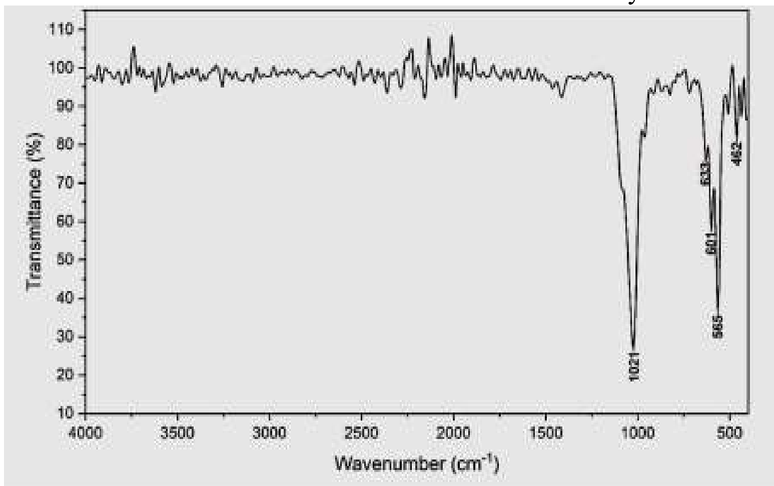

Figure 2: Wave numbers of Nano-HAp powder synthesized from biogenic marine shells.

Table 3: IR spectra displaying wave numbers and assignments of the Nano-HAp powder. (19)

Wave number (cm^{-1})	Peak Assignment
1021	Triply degenerated asymmetric stretching mode, ν_3c of the P-O bond in the phosphate group $(PO_4)^{3-}$
962	Non-degenerated asymmetric stretching mode, ν_1 of the P-O bond in the phosphate group $(PO_4)^{3-}$
633	Vibration mode, ν_L of the hydroxyl group (-OH)
601	Triply degenerated mode, ν_{4a} of the O-P-O bonds in the phosphate group $(PO_4)^{3-}$
565	Triply degenerated mode, ν_{4c} of the phosphate group $(PO_4)^{3-}$
462	Doubly degenerated mode, ν_{2a} of the phosphate group $(PO_4)^{3-}$

3. EDX Analysis of the Nano-HAp:

Elemental analysis of Nano-HAp of calcium, phosphorus, oxygen, and carbon was 23.3 at. %, 9.7 at. %, 48.8 at. %, and 17.9 at. % respectively (Figure 3).

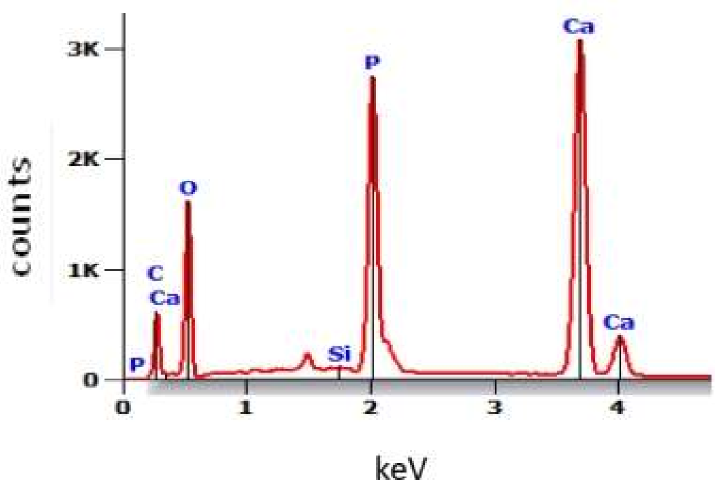

Figure 3: Elemental analysis of Nano-HAp powder

Scanning electron micrographs of the enamel surface at 3 different stages (1,2 and 3):

SE micrographs of untreated enamel surfaces showed a regular and intact surface of the flat polished enamel with the typical key-hole patterns of enamel prisms (Stage 1), (Figure 4).

SEM micrographs of the demineralized enamel surface showed an irregular surface and dissolved prism cores, indicating surface dissolution. Additionally, the surface showed a honeycomb pattern with a significant increase in surface porosities (Stage 2) (Figure 5).

SEM micrographs of the enamel surface after remineralization with Arabic Gum+ F-+ Nano-HAp showed a non-uniform mineral-rich layer deposited over the demineralized enamel, with some surface irregularities and microporosities. Cotton-like globular particles were observed on the enamel surface, along with partial coverage of the open prisms, indicating remineralization (Stage 3) (Figure 6).

SEM micrographs of the enamel surface after remineralization with MI Paste Plus showed that some enamel prisms maintained their morphology and most prism crystals have recovered. A mineral layer covered both prismatic and interprismatic enamel structures (Figure 7).

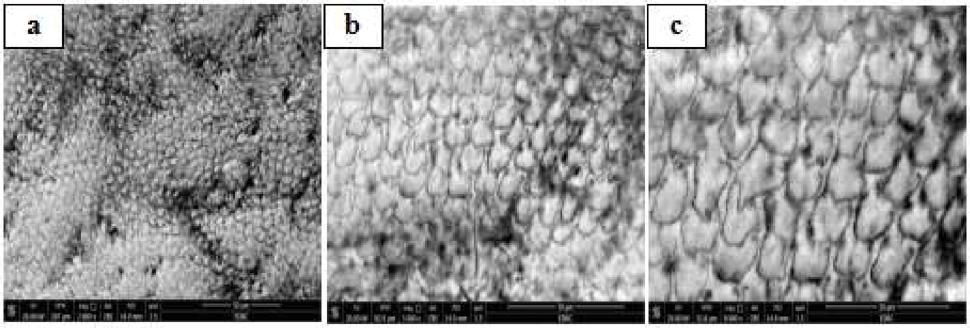

Figure 4: SE micrographs of untreated enamel surface at different magnifications; a. 2000x, b. 5000x and c. 8000x

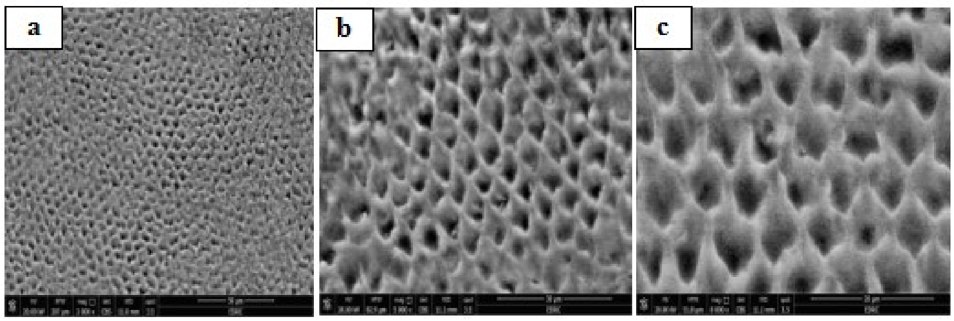

Figure 5: SE micrographs of demineralized enamel surface at different magnifications; a. 2000x, b. 5000x and c. 8000x.

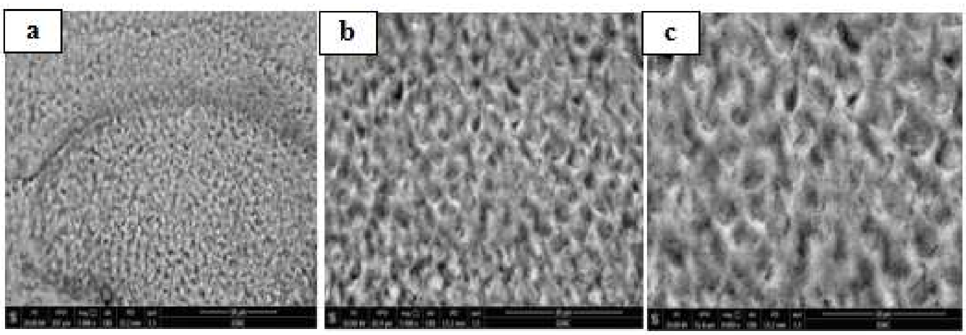

Figure 6: SE micrographs of enamel surface after remineralization with Arabic Gum + F- + Nano-HAp at different magnifications; a. 2000x, b. 5000x and c. 8000x.

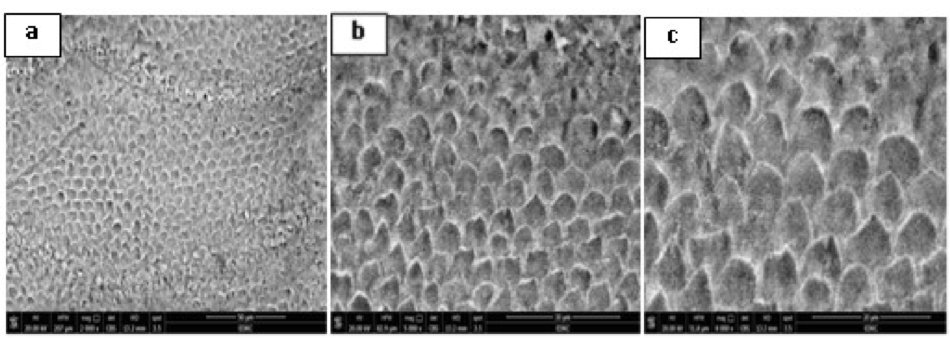

Figure 7: SE micrographs of enamel surface after remineralization with MI Paste Plus at different magnifications; a. 2000x, b. 5000x and c. 8000x.

Elemental analysis of Enamel surfaces of teeth:

The changes in Ca/P ratio in the different groups were summarized in (Table 4) and presented in (Figure 8). The results showed that there was no statistically significant difference in the mean Ca/P ratio between group A and group B across the three measurement stages. According to the remineralizing stage, group A exhibited a statistically significantly higher Ca/P ratio (1.82±0.03) than the demineralized group (1.63±0.07) and sound enamel (1.74±0.02). Group B displayed a statistically significantly higher Ca/P ratio (1.76±0.03) than the demineralized group (1.64±0.04) and a statistically significantly lower value than sound enamel (1.83±0.02).

Table 4: Comparisons and summary of Ca/P for the three measurement stages for both groups

Measurement stage	Ca/P (Mean±SD)		
	group A	group B	p-value
Baseline	$1.74{\pm}0.02^{Cc}$	$1.83{\pm}0.02^{Cc}$	**<0.001***
Demineralization	$1.63{\pm}0.07^{Bb}$	$1.64{\pm}0.04^{Bb}$	**0.002***
Remineralization	$1.82{\pm}0.03^{Ca}$	$1.76{\pm}0.03^{Ca}$	**<0.001***
p-value	**<0.001***	**<0.001***	

Values with different uppercase and lowercase superscripts within the same row and column, respectively, are significantly different; * significant (p<0.05).

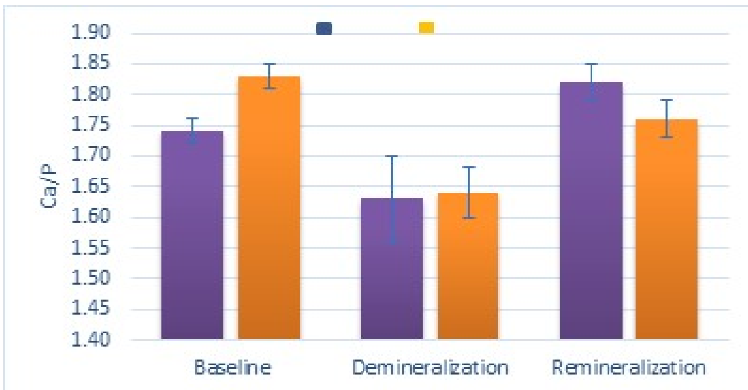

Figure 8: Bar chart displaying the mean and standard deviation values of Ca/P for group A and group B at three measurement stages.

DISCUSSION

Nowadays, the aim of modern dentistry is to manage early carious lesions non-invasively to prevent disease progression and improve aesthetics, strength, and function.(20)

In this study, Arabic Gum was added to Nano-HAp synthesized from biogenic marine shells to enhance their effectiveness. 500 ppm of fluoride ions was also included to accelerate enamel repair and transform weak hydroxyapatite into acid-resistant fluorapatite. (21)

To the best of our knowledge, this study is considered the first to evaluate the complex effect of Arabic Gum combined with fluoride ions alongside Nano-HAp in the remineralization of initial carious lesions.

The addition of calcium and phosphate to Arabic Gum in the remineralization solution was previously suggested as an extra source of minerals, enhancing its remineralizing potential. (22,23) So, in this study, we added Nano-HAp to Arabic Gum, which, in turn, achieved the required synergistic action and could resist acidic challenges.

After remineralization treatment, both groups showed a significant increase in Ca/P ratio (p<0.05) compared to the demineralizing stage. They demonstrated a remineralizing ability despite the acidic challenges conducted during the 14-day period.

In Group A, SE micrographs revealed a dispersed mineral deposit on the demineralized enamel surface, with a Ca/P ratio that was insignificant compared to Group B. Increased calcium levels in Nano-HAp can limit the acid challenge, contributing to an enamel mineral oversaturation state. (24)

Nano-HAp particles promote greater mineral accumulation in the outer layer of carious lesions, resulting in a highly mineralized external layer. (25)

Our findings aligned with the results indicating additional benefits of Nano-HAp addition into fluoridated toothpaste on carious lesion surfaces. The Nano-HAp fluoride toothpaste showed a consistent increase in surface hardness and a notable reduction in surface roughness compared to the standard fluoride control. (26) Another study proved better results of Nano-HAp compared to tricalcium phosphate, with differences being insignificant. (27)

Kim et al. evaluated the combined effects of Nano-HAp and fluoride mouthrinse on an early carious lesion. The study suggested that Nano-HAp plays a synergistic role in remineralization with a fluoride mouthrinse. If sodium fluoride reacts with Nano-HAp, this reaction could produce fluoroapatite and sodium hydroxide. Because sodium hydroxide raises the pH, the overall pH of the treatment solution would increase with higher Nano-HAp concentrations in the NaF solution. This might explain the synergistic remineralizing effects of Nano-HAp with NaF solution. (28)

The rate and amount of Nano-HAp precipitation increased with higher concentrations, as there was an increase in the deposition of calcium and phosphate ions. (29) A concentration of 1% Nano-HAp was used in this study. From a practical perspective, it is not advisable to use high Nano-HAp concentrations with high-molecular-weight Arabic Gum. It leads to the formation of a highly mineralized enamel layer on the surface. This can limit the total remineralization of the lesion, resulting in a "superficially healed" tooth with underlying demineralization. (26)

Conversely, a previous study reported that Nano-HAp did not decrease demineralization in bovine enamel. (30) This may be caused by the highly remineralized outer enamel surface, which prevented the diffusion of mineral ions into its deeper layers, limiting enamel recrystallization. (26) Another pH cycling study found that combining fluoride and Nano-HAp did not produce any synergistic effect. A dentifrice containing 10% Nano-HAp, with or without additional fluoride, showed similar remineralization effectiveness compared to fluoride-containing dentifrices. (31)

The Ca and P atomic % increase significantly in Group B (MI Paste Plus) compared to the demineralization stage. This may be attributed to the sticky nature of CPP, which binds to the tooth surface. This provides a reservoir of bioavailable calcium and phosphorus for both tooth surfaces and saliva. The anticariogenic effect of CPP-ACP was achieved by increasing Ca and P levels, which reduced tooth demineralization and enhanced remineralization. (32)

Talaat et al. reported that Nano-HAp and CPP-ACPF pastes are effective in rehardening initial enamel carious lesions in young permanent teeth. There was no significant difference in surface microhardness between both groups. (33)

CONCLUSION

Within the limitations of this in vitro study, these findings suggest that the synthesized Nano-HAp effectively remineralizes incipient enamel carious lesions when combined with Arabic Gum and fluoride ions. It could be a promising, cost-effective alternative to commercially available remineralizing agents.

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