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Enhancement of Apatite Formation Ability of Mineral Trioxide Aggregates Using Bioactive Glass

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Abstract

Introduction: This study aims to assess the impact of adding Bioactive Glass (BG) to Mineral Trioxide Aggregate (MTA) to improve MTA's bioactivity and apatite formation ability. Since BG and MTA share similar bioactivity properties, it is hypothesized that a novel combination of the two mentioned materials could enhance MTA's apatite formation ability and ultimately its bioactivity behavior.

Methods: BG-MTA Samples were prepared with concentrations of 10 and 20 wt% BG and submerged in Simulated Body Fluid (SBF) to evaluate their compressive strength. The samples were then characterized using SEM, XRD, and FTIR after 3, 20, and 40 days of incubation.

Results: The findings suggest that adding BG to MTA can improve its apatite formation ability and overall bioactivity behavior. This hybrid approach could be a viable option for endodontic clinical application.

Discussion: MTA is a material used in dentistry for various procedures, such as root canal therapy and pulp capping. By enhancing the bioactivity of MTA using BG, it can improve its ability to stimulate the formation of new tissue and promote healing, which can lead to better clinical outcomes for patients.

Keywords: MTA, Bioactive glass, Bioactivity, Apatite

Introduction

Mineral trioxide aggregate (MTA) was developed at Loma Linda University in the 1990s (1). MTA has been used for root apex repair, pulp capping in reversible pulpitis, apexification, and as a root-end filling material because of its sealing ability (2.3). MTA has gained recognition as a valuable material for due to its excellent biocompatibility, leading to favorable clinical results (4). However, according to the literature, MTA has some significant drawbacks such as Poor physical behavior (5), long setting time (6.7), and weak handling behaviors (8) that still need to be addressed (9-11). According to the reports, modification of MTA with additives such as calcium lactate gluconate (8), calcium chloride (12), and sodium hydrogen phosphate (13) has been able to overcome some of its shortages.

In most clinical application environments of MTA, more than one surface of the MTA material is in contact with the periodontal tissue. When the unset MTA is contaminated with surrounding blood the mechanical behavior of MTA is unfavorably affected (14). Therefore, it seems that enhancing the apatite formation ability of MTA (15) and improving its surface morphological structure (16) can be effective in the fabrication of more calcified structures of MTA after applying endodontic treatments. Bioactive glass (BG) which was introduced by L. Hench at the University of Florida in 1969 (17) could be a proper candidate to reach this target. As a bioactive ceramic material (18), 45S5 BG is composed of 45 wt% , 24.5 wt% , 24.5 wt% and 6.0 wt% . When BG encounters simulated body fluid (SBF), it immediately undergoes ionic dissolution and glass degradation. Silica ions are released, forming a silica-rich layer on the surface. Outside this layer, calcium and phosphoric acid in the body fluid form a layer of calcium phosphate, which becomes hydroxyapatite when it crystallizes (19). Further, BG makes a desired interaction with host tissue and bonds to mineralized; This causes faster hydroxyapatite formation ability and a higher dissolution rate (19,20). Due to the biocompatibility and apatite formation ability of ceramics (21), several studies have been conducted using ceramics as an additive materials in dental restorative materials such as composite resin (22), glass ionomer cement (23), and even surface treatment of dental implants (24.26), however, So far few studies have been conducted on adding BG to MTA with the aim of increasing the apatite formation ability. This study aimed to evaluate the impact of adding BG on the apatite formation ability of MTA by examining the characterization of MTA supplemented with BG.

Materials and Methods

Material preparation

White ProRoot MTA (Salamifar Dental Supply, Tehran, Iran) was used as the control group and named as MTA. The main components of MTA powder were tricalcium silicate (Ca3SiO5), dicalcium silicate (Ca2SiO4), tricalcium aluminate (Ca3Al2O6), bismuth oxide (Bi2O3) and calcium sulfate (CaSO4). The 45S5 BG (45 wt% , .5 wt% , 24.5 wt% and 6.0 wt%) was preparade using Sol-gel method (27). The 45S5 BG is obtained from precursors TEOS: $Si(OC_2H_5)_4$ (for SiO_2 oxide), CNT: $Ca(NO_3)_2$,$4H_2O$ (for CaO oxide), TEP: PO_4 $(C_2H_5)_3$ (for P_2O_5 oxide), and $NaNO_3$ (for Na_2O oxide); (FUJIFILM Wako, Pure Chemical Corp, Japan). The BG powder was ball-milled (particle size less than 50 µm) and added to MTA at 10 wt% and 20 wt% concentrations; these were named as 10BG-MTA, and 20BG-MTA. Based on the manufacturer's recommendations, the L/P ratio was adjusted to 0.3. The SBF was prepared according to the previous study (28). All the samples (including the control group and modified groups) were stored in SBF at 37 °C for 3, 20, and 40 days. Albeit, to ensure successful synthesis and its composition before inclusion in MTA, the 45S5 BG was characterized. After each storage period, excess water in the samples was removed with filter paper and dried; the samples were examined for apatite-forming ability by SEM (Scanning Electron Microscopy), XRD (X-ray Diffraction), and FTIR (Fourier Transform Infrared Spectroscopy).

Preparation of SBF

The SBF was prepared by incorporation of NaHCO3, MgCl2.6H2O, NaCl, KCl, KH2PO4, and CaCl2 into DW; buffered to pH=7.25 with TRIS

and HCl 1N at 37°C. Its composition is listed in Table 1 and compared with human blood plasma (29).

Table 1. Composition of human blood plasma (inorganic part) and SBF (mmol/l)

Ion	SBF (mmol/l)	Plasma (mmol/l)
Mg^{+2}	1.5	1.5
K^{+}	5.0	5.0
Na^{+}	142.0	142.0
Cl^{-}	136.8	107.0
Ca^{+2}	2.5	2.5
SO_4^{-2}	0.5	0.5
HCO_3^{-2}	5.3	26.0
HPO_4^{-2}	1.0	1.0

Characterization studies

SEM

The surface morphology of the BG-MTA, and 20BG-MTA was observed using a SEM (MIRA3 FEG-SEM, Tescan, Czech Republic) at the accelerating voltage of 15 kV after the conventional gold sputtering. SEM observation study was performed on all samples after 3, 20, and 40 days of SBF storage.

Compressive strength

The compressive strength analysis of the materials followed the ISO 9917-1 method (30). The specimens in various preparation conditions (MTA, 10BG-MTA, and 20BG-MTA) were mixed and placed in an acrylic mold with specific dimensions of 3.5 mm in diameter and 5.0 mm in height. Following placement, the entire assembly including mold and materials was moved to an incubator set at 37 °C with 95% humidity. It remained in this environment for one day to allow for a perfect setting. Subsequently, the specimens were then removed from the mold and immersed in an SBF solution for 3 and 7 days at 37°C, with regular SBF solution replacement of every 2 days. The compressive strength was determined by subjecting the specimens to a Universal Testing Machine (Instron 5566S, Canton, MA, USA) at a crosshead speed of 2 mm/min. The experiment involved measuring and recording the maximum load required to fracture each specimen, followed by the calculation of its compressive strength.

XRD

The phase structure of the samples, before and after treatment by BG, was investigated using an XRD (ADVANCE D8, Bruker, Germany). The diffractometer operated at 40 kV and 40 mA, with radiation at a wavelength of 1.5405 A°. The examination time for all groups was 3, 20, and 40 days of SBF storage.

FTIR

FTIR (Bruker Optik GmbH, Ettlingen, Germany) was used to investigate the chemical bands formed in the samples. For FTIR analysis, 600 µg of each sample (pure MTA, 10BG-MTA, and 20BG-MTA) was carefully mixed with 250 mg KBr powder and pelleted under vacuum. Finally, the pellets were analyzed in the spectral range from 400 to 1400 cm^{-1} at the scan speed of 23 scan/min with 4 cm^{-1} resolution. The investigation time for all groups was 3, 20, and 40 days after immersion in SBF.

Statistical analysis

The data was analyzed using descriptive statistical methods with SPSS 14 software. The normality of the bioactivity in the experimental groups at different times was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Levene test was used to assess the homogeneity of variance of the bioactivity samples at different times. An analysis of variance tests with repeated measures (ANOVA) was conducted to examine the mean bioactivity of the experimental groups. A significance level of $p < 0.05$ (*) was considered.

Results and discussion

Characterization of the samples before and after treatment

The bioactivity of MTA has been proven in laboratory

and clinical investigations in a number of endodontic treatment indications. However, as was already indicated, there are several drawbacks to MTA that must be addressed, such as its poor handling characteristics and prolonged setting time [8.11]. To address these flaws, we investigated the use of BG as an additive in MTA powder, which has been reported as a bioactive material with apatite transforming potential. We examined the effect of BG on the apatite formation ability of MTA and demonstrated that MTA containing BG had better apatite formation ability in SBF conditions. The benefits of BG's excellent bioactivity have recently been highlighted by various studies (24.26.31). To our knowledge, only a few studies examined the effect of BG supplementation on MTA bioactivity [23]. In the present study, we investigated varied times of BG-MTA immersion in SBF and discovered that supplementing MTA with different concentrations of BG was efficient in enhancing MTA's apatite formation capacity, which differed significantly from the previous study.

SEM

Fig. 1 (a)-(c) shows the SEM micrographs of the MTA (Fig. 1(a, A)), 10BG-MTA (Fig. 1(b, B)), and 20BG-MTA (Fig. 1(c, C)) after 3, 20, and 40 days of storage in SBF. As can be seen, the first apatite formation developed in just 3 days of immersion in SBF for all the samples. However, 20BG-MTA sample is completely covered with newly formed layer even after 3 days of storage is SBF. With increasing immersion time, a layer consisting of flake-shaped Particles grew and fully covered the surface of all the samples; that is, the amount of apatite crystals increased with the immersion time. After 40 days, this is also confirmed by SEM micrographs of MTA, 10BG-MTA, and 20BG-MTA, where SEM depicts that a dense deposit cover and apatite layers were further thickened. The SEM observation test in this study was a useful method for assessing the prepared samples' capacity to transform into apatite formation. According to Fig. 1, the first apatite crystals formed in all samples after only 3 days of immersion in SBF. However, after 3 days, the amount of apatite formed by 20BG-MTA was more than that of 10BG-MTA and MTA. After 20, and 40 days of immersion, MTA, 10BGMTA, and 20BG-MTA's surfaces were completely covered by flake-shaped apatite Particles. Apatite crystal formation increased with immersion time as was to be predicted. However, compared to had a large amount of apatite formation. This can be seen in the SEM micrographs of the sample that was submerged in SBF for 20, and 40 days, where SEM shows that dense deposits cover and apatite layers were further thickened. According to the SEM, BG, as an additional bioactive material, boosts MTA's apatite -forming capacity. Because BG has a sufficient amount of silica self-agglomeration (23). Furthermore, the bioactivity of BG and its ability to transform apatite may be related to the release of calcium and phosphorus (24). As a result of the beneficial properties of BG materials and the fact that BG has the full potential to cause intercellular reactions after exposure to biological fluids, MTA supplemented with BG was able to enhance its own apatite formation ability, which is directly related to its bioactivity.

Compressive strength

The compressive strength (n=8) results are presented in Fig. 2. Comparing the specimens stored in SBF for 3 and 7 days, the non-modified MTA group exhibited slightly higher compressive strength than the MTA and

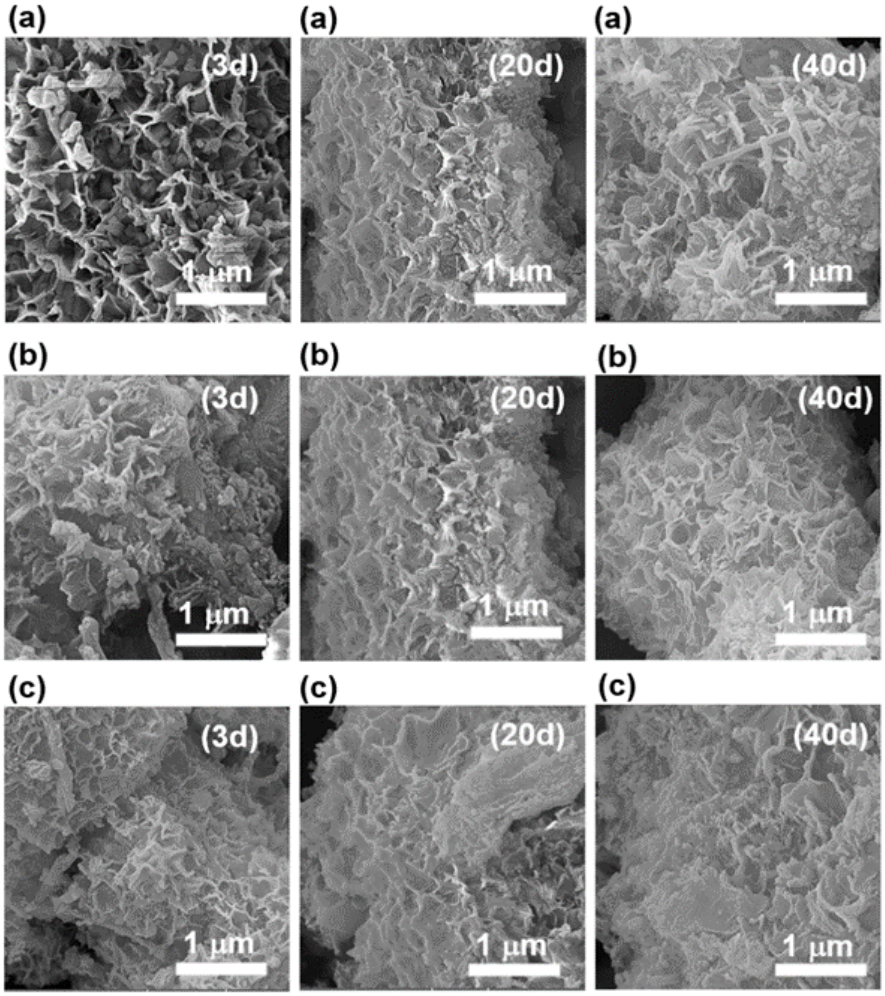

Fig. 1. SEM micrographs of the MTA (a), 10BG-MTA (b), 20BG-MTA (c) after of immersion in SBF.

10BG-MTA and 20BG-MTA groups upon 3 days. However, there was no significant difference in the strength between these groups. Additionally, after 7 days of storage in SBF, all groups showed similar compressive strength intensities with no statistically significant differences observed. ($p > 0.05$). The assessment of compressive strength is a crucial factor in the evaluation of restorative MTA (25). In this regard, to determine the efficacy of BG supplementation SBF, a comparative experiment was conducted. The results indicated that the compressive strength values of the BG-supplemented MTA groups did not significantly differ from the control group (MTA). Although the presence of BG compensated for the reduction in compressive strength caused by SBF, the slight decrease did not render MTA weaker, and there was no significant difference in the compressive strength of groups. The slight reduction of 10BG-MTA and 20BG-MTA can be attributed to the fragile nature of the glass composition in BG, which contributes to its poor mechanical properties. Even though the bioactivity of dental materials for perforation repair is an important characteristic and the apatite formation ability of MTA is improved by adding a specific concentration of BG, additional research on compressive strength and mechanical properties is still needed to improve various characterization properties of MTA at a specific concentration of BG-MTA.

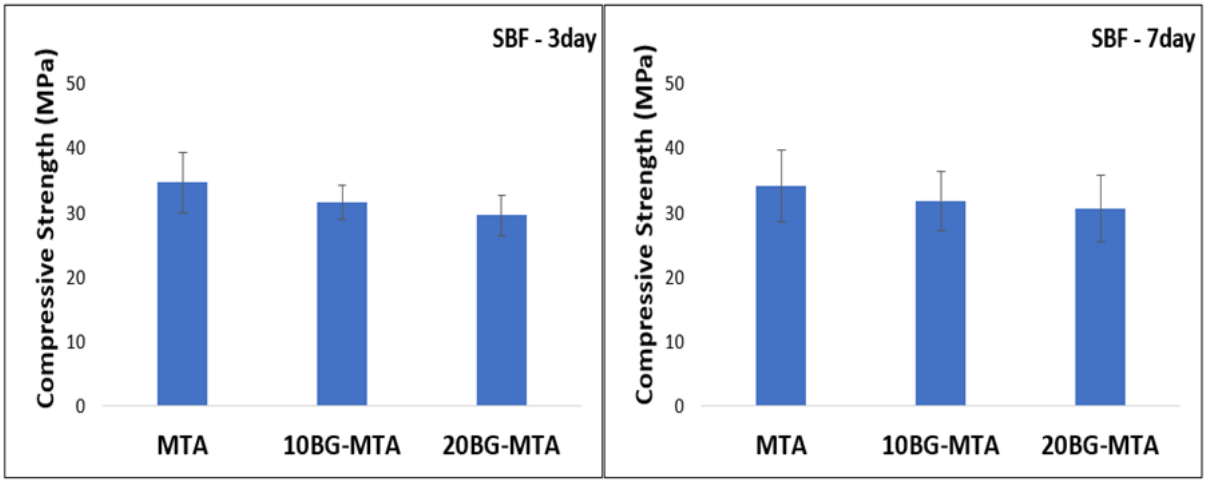

Fig. 2. Results of experimental groups, MTA, 10BG-MTA, and 20BG-MTA, in SBF storage solution for 3, and 7 days.

XRD

Fig. 3a (a)-(c) and Fig. 3b (a)-(c) and Fig. 3c (a)-(c) exhibit the XRD patterns of the pure MTA, 10BG-MTA, and 20BG-MTA samples after 3, 20, and 40 days of immersion in SBF. As can be seen, after 3 days of SBF storage, two peaks are located at 26°, and 32°; which were assigned to be (211), (002) apatite according to the standard JCPDS cards (#09-0432). However, the apatite peak intensities detected in the 26° and 32° regions for the treated samples, 10BG-MTA and 20BG-MTA, were higher than that of the untreated MTA sample. After 20 days of immersion, the two peaks detected for apatite became more apparent; that is, the process of apatite formation is still taking place. The apatite peak intensities of the experimental groups after 20 days were as follows: MTA < 10BG-MTA < 20BG-MTA. Furthermore, As can be seen in the patterns (Fig. 3c), upon 40 days of investigation, the intensity and broadness of the apatite peaks detected for 20BG-MTA is higher than that of 10BG-MTA, and MTA. XRD analysis was applied to assess the existence of apatite formation in the MTA, 10BG-MTA, and 20BG-MTA after 3, 20, and days of immersion in SBF (Fig. 3a) (Fig. 3b) (Fig. 3c). Throughout the experiment, the 26° and 32° peaks grew in the MTA, 10BG-MTA, and 20BG-MTA groups. Despite the fact that XRD only studies surface components, it was discovered that MTA supplemented with BG has been shown to generate more hydroxyapatite than pure MTA. Furthermore, the small decrease in the intensity of apatite peaks in all samples after 40 days could be attributed to partial hydroxyapatite dissolution in SBF caused by long-term storage.

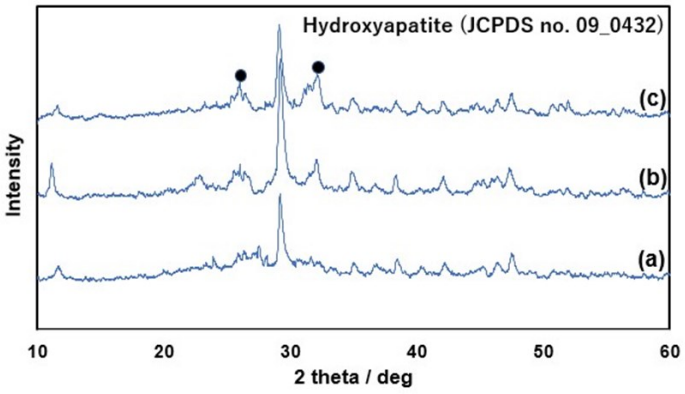

Fig 3a. XRD patterns of the MTA (a), 10BG-MTA (b), and 20BG -MTA (c) after 3 days of immersion in SBF.

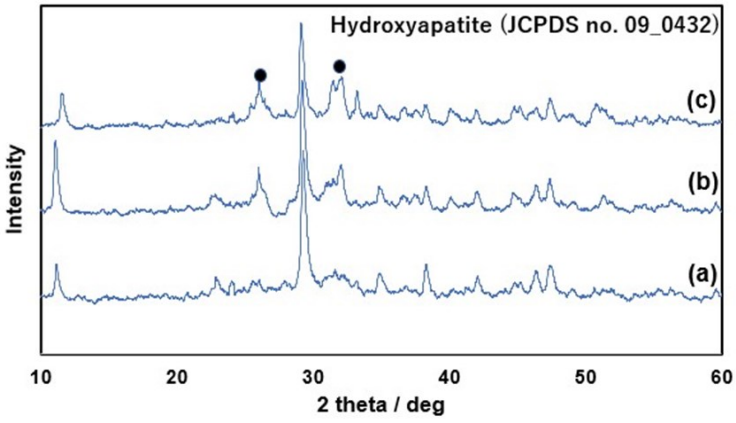

Fig. 3b. XRD patterns of the MTA (a), 10BG-MTA (b), and 20BG-MTA (c) after 20 days of immersion in SBF.

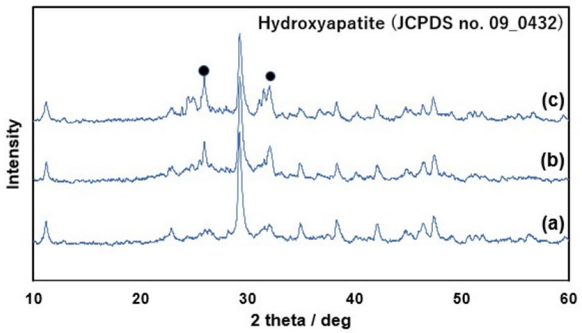

Fig. 3c. XRD patterns of the MTA (a), 10BG-MTA (b), and 20BG-MTA (c) after 40 days of immersion in SBF.

FTIR

According to the Fig. 4a (a)-(c), the formation of apatite on the surface of the specimens was observed in the spectra. The band at around 560 and 605 cm^{-1} corresponds to the apatite phosphate (P-O) band and can be seen in all the samples. At about 1000-1150 cm^{-1}, the P-O band also exhibits an asymmetric stretching vibration. FTIR spectra analysis was used to identify the chemical bands of experimental groups. The apatite phosphate (P-O) band can be found in all samples and is located between 560 and 605 cm-1. According to the FTIR test, with the period of investigation time, the level of hydroxyapatite formation has increased. However, after 40 days of investigation, the amount of hydroxyapatite in all samples was reduced. Within our

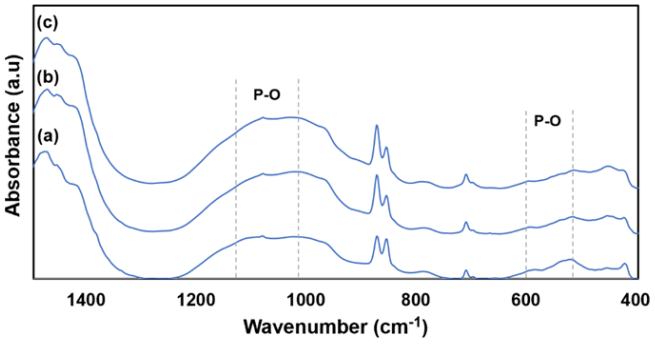

Fig. 4a (a)-(c) shows FTIR spectra of the samples; MTA, 10BG-MTA, and 20BG-MTA, after 3 days of immersion in the SBF.

knowledge and based on the current study, the results clearly revealed that adding BG to MTA increases its apatite formation ability, resulting in its bioactivity and that this intensification can continue over time (by 40 days). The reason for this intensification can be attributed to BG's ternary main components, Ca, P, and Si, which have intensified the bioactivity of MTA.

FTIR spectra of the MTA, 10BG-MTA, and 20BG-MTA, after 20, and 40 days of SBF storag (Fig. 4b)

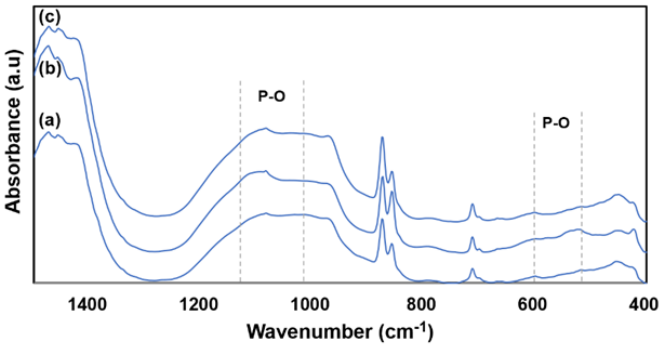

Fig. 4b. FTIR spectra of the MTA (a), 10BG-MTA (b), and 20BG -MTA (c) specimens after 20 days of immersion in the SBF.

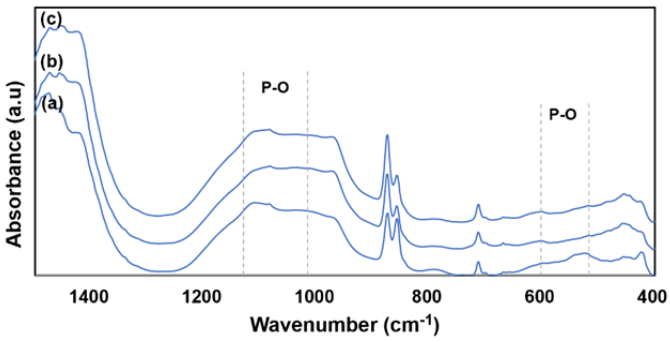

Fig. 4c. FTIR spectra of the MTA (a), 10BG-MTA (b), and 20BG -MTA (c) specimens after 40 days of SBF storage.

Table 2. Mean and standard deviation of the apatite formation amount of the samples upon 3, 20, and 40 days of investigation.

Time	Group	Average	Standard Deviation
3 days	MTA	0.06000	0.001871
	10BG-MTA	0.18900	0.001871
	20BG-MTA	0.20300	0.006964
	all	0.15067	0.066743
20 days	MTA	0.18500	0.004743
	10BG-MTA	0.34400	0.002550
	20BG-MTA	0.38900	0.007176
	all	0.30600	0.090708
40 days	MTA	0.19000	0.002550
	10BG-MTA	0.27900	0.000707
	20BG-MTA	0.28100	0.003674
	all	0.25000	0.043990

The pecks at 560 and 605 cm^{-1} are due to the bending vibration of P-O, and these similar peaks are visible in the FTIR of all the samples. The P-O band also has an asymmetric stretching vibration at around 1000-1150 cm^{-1}. The average bioactivity (apatite formation ability) of the samples after 3, 20, and 40 days of immersion in SBF. As it is clear, the apatite formation ability in the modified samples with BG is higher than that of unmodified sample Fig 5.

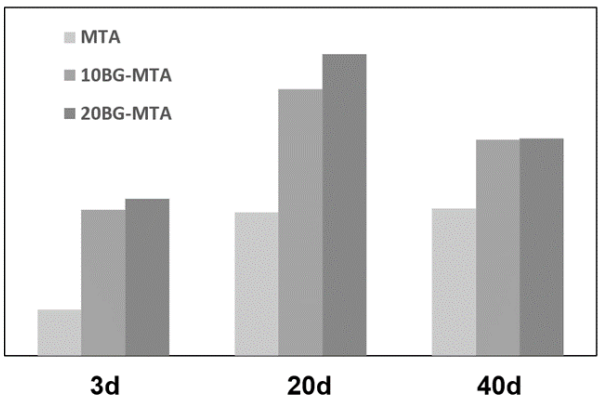

Fig. 5. Apatite transformation ability of specimens after 3, 20, and 40 days of immersion in the SBF: MTA, 10BG-MTA, and 20BG-MTA.

The results of Kolmogorov-Smirnov and Shapiro-Wilk tests which were used to evaluate the normality of the bioactivity of the samples at different times. (P-value>0.05) (Table 3)

Table 3. Results of Kolmogorov-Smirnov and Shapiro-Wilk tests upon 3, 20, and 40 days of investigation. P-value>0.05

Time	Group	Kolmogorov-Smirnov P-value	Shapiro-Wilk P-value
3 days	MTA	0.161	0.453
	10BG-MTA	0.161	0.453
	20BG-MTA	0.200	0.994
20 days	MTA	0.161	0.168
	10BG-MTA	0.161	0.537
	20BG-MTA	0.161	0.171
40 days	MTA	0.161	0.537
	10BG-MTA	0.161	0.325
	20BG-MTA	0.200	0.787

The results of the Kolmogorov-Smirnov and Shapiro-Wilk tests showed the variable distribution of bioactivity of the samples at different times and groups is normal. Therefore, based on the results, the Levene test, a parametric test, was used to investigate the effect of BG additives on the enhancement of MTA bioactivity. This was done by assessing the homogeneity of variance of the bioactivity samples. On the other words, the Levene test was used to determine if the variances of groups were equal or not. (P-value>0.05)

the results of the Levene test. The test revealed that 3 days after the study commenced, the hypothesis of equality of variance was rejected at a significance level of 0.05. At times 20 and 40 after the study began table 4. the hypothesis of equality of variance was not rejected at a significance level of 0.05. To evaluate the impact of the groups studied on the average bioactivity of the samples in three evaluation times, a Repeated Measures ANOVA test was conducted with a significance level of 0.05. The results are presented in Table 5.

Table 4. Results of Levene test upon 3, 20, and 40 days of investigation. P-value>0.05

Evaluation time	P-value
3 days	0.036
20 days	0.372
40 days	0.090

Table 5. Results of analysis of variance with repeated measures (Repeated measures ANOVA).

Source of variability	P-Value*
Group	0.001>
Evaluation time	0.001>
Interaction between group and evaluation time	0.001>

Statistically significant difference between the mean bioactivity of the samples in the three groups.) P-Value<0.001)(table 5) Therefore the Sidak test was used to determine exactly which of the two groups differed. The results of this evaluation are presented in Table 6.

Table 6. Sidak test results (experimental groups evaluation)

Group (I)	Group (J)	Average Differences (I-J)	P-value
20BG-MTA	10BG-MTA	0.02640	0.001>
	MTA	0.17360	0.001>
10BG-MTA	MTA	0.14720	0.001>

The results of the Sidak test, Table 6, showed that there is a statistically significant difference between the mean bioactivity of the samples in the group, 20BG-MTA, with both groups of MTA and 10BG-MTA and the mean bioactivity of 20BG-MTA was higher than that of the average in both groups, MTA and 10BG-MTA. In addition, there was a statistically significant

difference between the mean bioactivity of the 10BG-MTA group and the mean bioactivity of the MTA g and the mean bioactivity of the 10BG-MTA was higher than the average of the samples of the MTA group. Furthermore, there was a statistically significant difference between the mean bioactivity of the samples in the three evaluation times. Sidak test was used to determine exactly which of the two evaluation times differed. The results of this evaluation are presented in Table 7.

Table 7. Sidak test results (time evaluation).

Evaluation time (I)	Evaluation time (J)	Average differences (I-J)	P-value
After 3 days	After 20 days	-0.155	0.001>
	After 40 days	-0.099	0.001>
After 20 days	After 40 days	0.056	0.001>

The results from Table 7 indicate a significant difference in the mean bioactivity of the samples at different evaluation times. Specifically, the mean bioactivity at 3 days was lower compared to both 20 and 40 days. Additionally, there was a statistically significant difference between the mean bioactivity at 20 days and 40 days. These findings suggest an interaction between the experimental groups and evaluation times, indicating that the effect of the experimental groups on the average bioactivity varies across the three evaluation times (p-value < 0.05).

To further examine the effect of the experimental groups on the mean bioactivity at each evaluation time, a one-way analysis of test variance was performed for each evaluation time. As it was expected the results of one-way analysis of test variance confirmed that there is a significant difference in the mean bioactivity of experimental groups at various investigation times. Furthermore, Sidak and Games-Howell post hoc tests were examined to investigate the difference between the two groups according to the results of Table 4. The result of this test is given in Table 8.

Table 8. Results of Sidak and Games-Howell post hoc tests.

Groups		After 3 days		After 20 days		After 40 days	
Group (I)	Group (J)	Average differences (I-J)	P-value*	Average differences (I-J)	P-value*	Average differences (I-J)	P-value*
20BG-MTA	10BG-MTA	0.014000	0.020	0.045000	<0.001	0.002000	0.578
	MTA	0.0143000	<0.001	0.204000	<0.001	0.091000	<0.001
10BG-MTA	MTA	0.129000	<0.001	0.159000	<0.001	0.089000	<0.001

The results of this study showed that upon 3, and 20 days of investigation, there was a statistically significant difference between the mean bioactivity of the samples in the group 20BG-MTA with both groups MTA and 10BG-MTA; and the mean bioactivity of the samples in the group 20BG-MTA was more than both groups MTA and 10BG-MTA. Furthermore, there was a statistically significant difference between the mean bioactivity of the samples in the 10BG-MTA and MTA. That is; 10BG-MTA presented a higher bioactivity than the MTA. Furthermore, 40 days into the study, there was a notable contrast in the average bioactivity of the MTA samples compared to both the 20BG-MTA and 10BG-MTA groups. The mean bioactivity of the MTA samples was lower than both other groups. However, there was no significant difference in the mean bioactivity between the 10BG-MTA and 20BG-MTA groups. Finally, it can be concluded that, since BG is known to release ions such as Ca, P, and Si, which can enhance the formation of apatite, the presence of these ions could promote the precipitation of apatite crystals, which is a key component of MTA. Additionally, based on the obtained results of this study, BG increased the alkalinity of the surrounding environment, which can further promote the formation of apatite. The interaction between BG and MTA involves the release of ions from the BG, which can react with the MTA to form a composite material. The resulting MTA-BG composite material was shown to have improved bioactive properties compared to MTA alone, making it a promising material for use in various dental applications.

This theoretical investigation contributes to the development of innovative approaches in the field of biomaterials and tissue engineering, with potential implications for improving dental and orthopedic treatments.

Conclusions

Although pure MTA showed apatite formation capacity and is known as a bioactive material, Increased hydroxyapatite leaks were seen in the BG-supplemented MTA group under SBF storage conditions. Furthermore, this study demonstrated that the maximal period of apatite production in SBF conditions could not exceed 40 days. MTA supplemented with BG could be used as a potential biocompatible restorative material for clinical endodontics because the formation of hydroxyapatite increased under the SBF condition.

Conflict of interest

The authors declare that they have no competing interests.

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