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SURFACE NANO-ROUGHNESS OF BIOACTIVE GLASS NANOPARTICLES COATING ON TITANIUM IMPLANTS (IN-VITRO STUDY)

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ABSTRACT:

INTRODUCTION: Titanium is an optimal choice for dental implants. However, lack of surface bioactivity is limiting its use, especially in medically compromised patients, among whom insufficient osseointegration is more prevalent. Coating by bioactive glass can improve their efficacy leading to better implant-to-bone bonding, particularly 70S30C being the most bioactive among the binary calcium silicate glass systems. Nanoparticle coatings induce osteoblastic cell attachment and proliferation, have good affinity to bone and possess stronger interfacial bonding to substrate.

OBJECTIVES: The aim of the current study was to develop a surface coating of sol-gel 70S30C bioactive glass nanoparticles on titanium dental implants, and to characterize the resultant coating from the standpoint of nano-roughness.

METHODOLOGY: Bioactive glass (BAG) was prepared using modified sol-gel technique, then milled into nanoparticles. Particle size of resultant milled powder was measured by Transmission Electron Microscope. Grit-blasted/acid-etched titanium dental implants were coated with bioactive glass nanoparticles via electrophoretic deposition. Average surface nano-roughness of BAG coated implants was analyzed by Atomic Force Microscope.

RESULTS: Bioactive glass nanoparticles showed particle size of <20 nm in diameter. There was statistically insignificant difference in average surface nano-roughness between uncoated and BAG coated implants. Although BAG did not increase the nano-roughness, results ensure that the coating has successfully conformed to and minimally affected grit blasted/acid-etched surface of uncoated implants on the nanoscale, originally set by the manufacturer to enhance osseointegration.

CONCLUSIONS: Coating titanium implants with 70S30C bioactive glass nanoparticles is attainable via electrophoretic deposition technique, resulting in homogenous coating, yet with no increase in nano-roughness.

KEY WORDS: Bioactive glass, Coating, Nanoparticles, Titanium Implant, Electrophoretic deposition.

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INTRODUCTION

The optimal core material for dental implants, regarding both clinical application and scientific research, is titanium due to its biocompatibility, minimal toxicity, excellent mechanical properties, and corrosion resistance. However, clinical applications of titanium implants are limited by the lack of their surface bioactivity.(1)

Bioactivity is the capability of implant material to interact and bond with living tissues. After implantation, a biological response is stimulated by the bioactive material resulting in a strong chemical bond "osseointegration" between implant and bone.(2)

Insufficient osseointegration occurs in 1-2% of healthy patients during the first few months and is considered as the main reason for implant failure.(3) However, dental implant therapy has appeared to be more challenging in medically compromised patients (diabetes, osteoporosis, bleeding disorders and hypothyroidism).(4, 5) Therefore, attempts are conducted to achieve more rapid and stable osseointegration.(1)

Osseointegration is influenced by many factors including: implant biocompatibility, fixture design, surface characteristics, surgical techniques, health state of host, biomechanical status, and time.(6)

Regarding surface characteristics, the hydrophilicity of titanium implants is affected by their surface chemical composition. Highly hydrophilic surfaces are more desirable than hydrophobic ones in view of their interactions with biological fluids, cells, and tissues.(7, 8) Moreover,

implant surface roughness is mandatory for osseointegration. Surface roughness increases implant surface area, improves cell attachment, induces presence of bone at the implant surface, and stimulates implant-bone biomechanical interaction.(8)

Titanium surfaces can be rendered active by some surface modifications; and therefore, enhancing cell proliferation for osseointegration. Various modifications have been developed to increase the surface roughness of dental implants, including subtractive and additive techniques.(9)
Subtractive techniques, known as surface treatment, can be mechanical (grit blasting), chemical (acid or alkaline etch), or electrochemical (anodization), all of which can modify the implant surface without adding a new material. They allow for changing the surface properties such as roughness, hydrophilicity, and morphology. Since no additional material is introduced to the surface, there is no possibility of detachment.(10)

On the other hand, additive techniques, known as coating, include enameling, plasma spraying, electrophoretic deposition (EPD), sol-gel coating (dip, spin or spray coating), and pulsed laser deposition.(11). They permit deposition of a thin film to replace the original surface with a new one. The main advantage of additive techniques is the presence of wider range of surface properties, whether chemical or physical, created by the new material. However, complete or partial detachment is the major drawback of the coating method.(9)

When compared to additive techniques, the effects of subtractive ones on surface properties are more limited. This is due to the biological effects exerted by additive techniques including the release of signal molecules, ions, or drugs to enhance bone quality as well as their antimicrobial features. Moreover, they accelerate osseointegration even in poor quality bone, protect from chemical corrosion exerted by body fluids, and reduce bacterial adhesion.(9)

Among additive techniques is EPD, a process where an electric field is used to make colloidal particles, suspended in a liquid medium, migrate and deposit onto a counter charged electrode.(12) Low cost, simple methodology, ability to produce coatings with variable thicknesses, high rate of deposition and ability to uniformly coat irregularly shaped or porous objects are the reported advantages of EPD. However, the main disadvantage of EPD is the need to densify the coating by postdeposition heat treatment.(12, 13)

The production of a surface with high and fast osseointegration capability is the major objective of surface coating, especially in medically compromised cases. Bioactive glass (BAG) and glass-ceramics are used clinically for tissue regeneration for their attractive properties, especially their high bioactivity.(14) Bioactivity of BAG is directly related to its dissolution rate, which is in turn indirectly related to the interconnectivity of its SiO_2 network. Upon implantation, dissolution of BAG occurs gradually, resulting in the growth of a carbonated hydroxyapatite (HCA) layer, which mimics the mineralized layer of natural bone. A chemical bond is formed when HCA layer is promoted at the surface by the released ions.(15)

Certain gene pathways can also be activated by BAGs, enhancing cell differentiation and osteogenesis. When compared with other bioresorbable inorganic materials, such as hydroxyapatite or other calcium phosphates, degradation of BAGs occurs rapidly, angiogenesis of newly formed tissues is promoted, and can be incorporated with antimicrobial agents. However, BAGs are limited by their brittle nature, which in turn limits their use for stress bearing applications.(16, 17)

Due to the pore size and volume of the gels associated with their large surface area, glass powders produced by sol– gel technique are more bioactive compared to the melt-derived glasses. In comparison with different gel glass compositions, a higher rate of HCA layer is formed with S70C30, together with more rapid initial dissolution and network disruption. S70C30 is found to be the most bioactive gel glass composition among the binary calcium silicate glass systems.(18, 19)

Improving osseointegration by incorporating nano-topological characteristics into implant surface modifications has been the new trend in recent years. Micro- and nano-structured coatings can be created by a variety of different coating methods using nanomaterials. The physical cues provided by the incorporation of micro/nanoparticles in a nano-topological surface may influence and control stem cell activity.(20)

Reducing the size of BAG into nanoparticles has become a primary aim in order to increase surface energy, improve material shaping versatility, and permit incorporation of various cell types. BAG nanoparticles (20-500 nm) are currently considered to be one of the very attractive materials for coating.(21, 22)

This study aimed to develop 70S30C BAG nanoparticle coating, prepared by modified sol-gel technique, on titanium implants by EPD, and to characterize its surface from the standpoint of average surface nano-roughness.

The null hypothesis of this study is that there will be no significant difference between coated and uncoated titanium implants regarding average surface nano-roughness.

MATERIALS AND METHODS

Bioactive glass preparation

Following the method published by Gadallah et al.(23), 70S30C BAG was prepared using modified

sol-gel technique. Polyethylene oxide ***(Sigma-Aldrich, Missouri, United States)***, urea ***(Loba Chemie, Mumbai, India)***, tetramethyl orthosilicate ***(Sigma-Aldrich, Missouri, United States)*** and calcium nitrate tetrahydrate ***(Loba Chemie, Mumbai, India)*** were added to acetic acid ***(Sigma-Aldrich, Missouri, United States)*** aqueous solution (0.01 N), and magnetically stirred ***(Hotplate and stirrer 1000, Jenway Ltd, United Kingdom)*** until completely dissolved. Two to three drops of hydrofluoric acid ***(Loba Chemie, Mumbai, India)*** which functioned as a gelation catalyst, was diluted with deionized water, and added to the solution which was then poured into multi-well plates and kept until complete gelation. The wet gel was aged at 40ºC, then immersed in deionized water, followed by ammonia for 24 h before being dried and thermally stabilized at 700ºC. The resultant scaffold was milled into nanoparticles using a planetary ball mill machine ***(PM 400, Retsch, Germany)***. Milling was performed at 350 rpm for 24 h using zirconium dioxide (ZrO_2) balls with glass/ball ratio of 1:9.(24)

Characterization of BAG nanoparticles

Particle size of the milled powder was measured using field emission transmission electron microscope ***(FE-TEM, JEM-2100F JEOL, Tokyo, Japan)***. BAG milled powder was first added to ethanol producing a dispersed solution which was sonicated for 15 min, then 5 µL of that solution was dropped on a carbon coated copper grid and left at room temperature until completely dried. TEM characterization was operated at 200 kV, and Gatan digital micrograph software was used for particle size measurements.

Coating of titanium implants with BAG nanoparticles

Electrophoretic deposition, with some modifications **(Fig. 1 A)** to the methodology previously published(23), was used to develop a surface coating of 70S30C BAG nanoparticles on dental implants ***(4.2 x 8 mm, OneQ-SL, Dentis Co. Ltd, Daegu, Korea)***, of grade 23 titanium (Ti-6Al-4V ELI, Titanium – 6% Aluminum – 4% Vanadium with extra low interstitials) with sandblasted, large grit, acid-etched (SLA) surface. The coating procedure started with magnetic stirring of 0.5 g BAG nanoparticles in 30 ml absolute ethanol for 5 minutes, then the suspension was agitated in a digital ultrasonic cleaner ***(CD-4820, Codyson, China)*** for 10 minutes **(Fig. 1 B)** to achieve non-agglomerated nanoparticles. EPD was performed using a cylindrical copper electrode (anode) 1 mm in thickness with an inner diameter of 36 mm, while the implant was positioned in the middle of the cylinder and connected as the cathode **(Fig. 1 C and D)**.(25, 26)

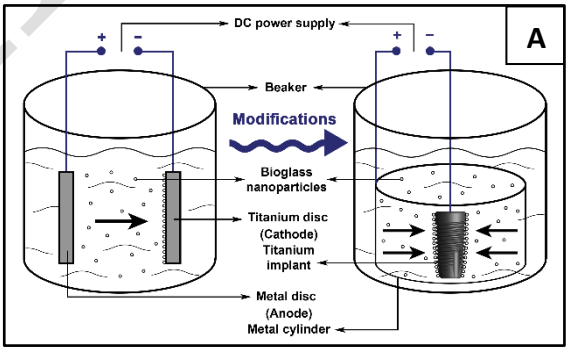
A direct current (DC) power supply ***(Maisheng MS-605D, China)*** was employed as a constant voltage source at 30 V for a duration of 60 s **(Fig. 1 E)**. Implants with the resulting coating were thermally treated in a vacuum compact tube furnace ***(GSL-1500X-50LVS, MTI Corp., Richmond, USA)*** at 700ºC for 2 h under argon with a heating and cooling rate of 2ºC/min **(Fig. 1 F)**. Coated implants were placed in a desiccator for isolation.

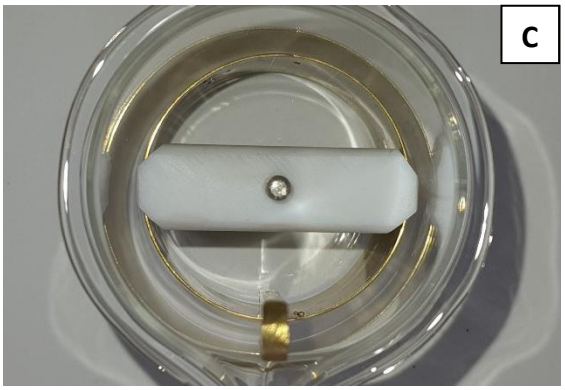
Nano-roughness analysis (Fig. 2)

Implants were scanned on the nanoscale using atomic force microscope ***(Scanning Probe Microscope SPM-9700, Shimadzu Co. Ltd, Kyoto, Japan)***, where they were placed on a custom-made base, 3D-printed by Formlabs 2 desktop 3D printer ***(Formlabs, Somerville, Massachusetts, United States)***, to be stable on the microscope sample table **(Fig. 2 B)**. Average surface nano-roughness (arithmetical mean height of a surface) was observed in dynamic non-contact mode in air. The observation area was set as 1 x 1 µm at an operating point of 0.298 V. This procedure was done with a rate of 1 Hz and phase gain of 0.001. Uncoated (control group; n=10) and BAG coated implants (test group; n=10) were scanned to evaluate the difference in surface nano-roughness.(27)

Statistical Analysis

Data were analyzed using IBM SPSS for Windows (Version 23.0) and significance was inferred at p value <0.05. Normality was checked for all variables using descriptive statistics, plots, and normality tests. All variables showed normal distribution; so, mean, standard deviation (SD), and 95% confidence interval (CI) were calculated, and parametric tests were used. Comparisons of surface roughness between uncoated and BAG coated implants were done using independent samples t-test.





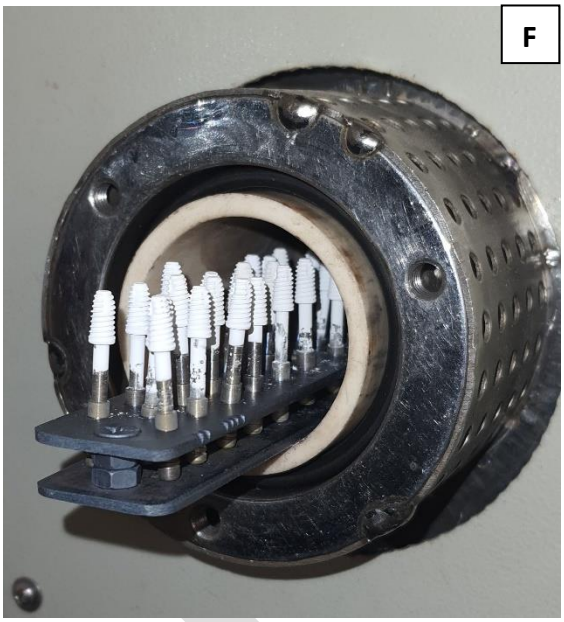
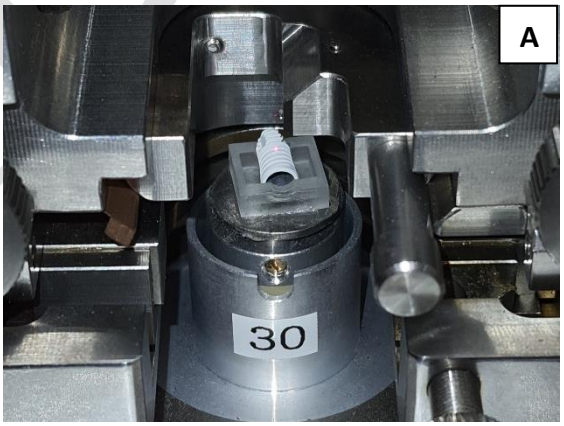


Figure 1: Coating of titanium implants with BAG nanoparticles. (A) diagram showing modifications made in EPD technique to coat a 3D complex object. (B) Ultrasonic agitation of the prepared suspension. (C and D) A close-up view for the EPD cell containing a cylindrical copper anode of 36 mm inner diameter and the implant coupled as the cathode in the center of the counter-electrode. (E) Electrophoretic deposition carried out under 30 V by DC power supply for 60 s. (F) Coated implants in compact tube furnace.



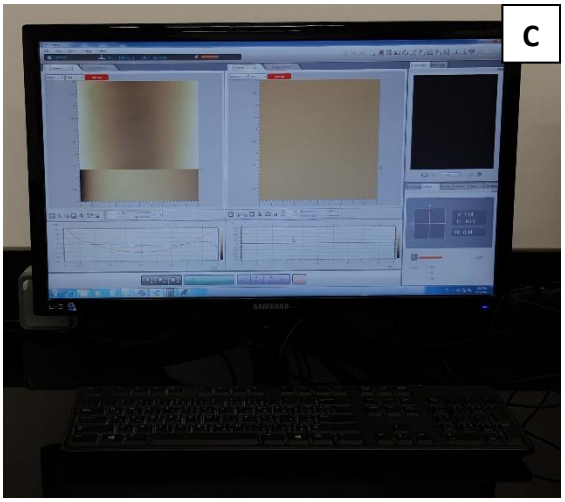


Figure 2: Nano-Roughness analysis. (A) Scanning of a BAG coated titanium dental implant via atomic force microscope. (B) Uncoated implant on a 3D-custom made base for stabilization during scanning. (C) Roughness data collection on the software.

RESULTS

Characterization of BAG nanoparticles

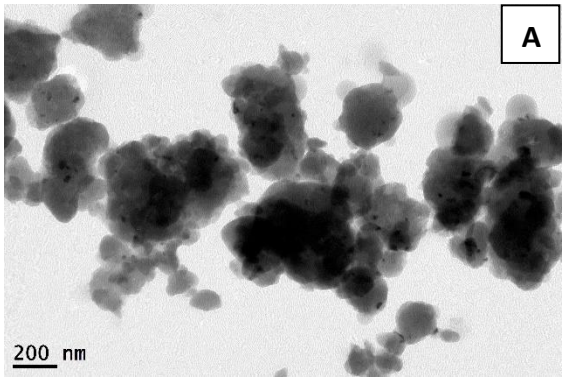
Particle size of the resultant milled BAG powder was measured via FE-TEM **(Fig. 3)** and found to be nanosized with particle diameter of less than 20 nm (4.87 to 15.24 nm). The nanoparticles strongly tended to form agglomerates, as they were clustered into larger aggregates, yet with more porous spaces and larger surface area.

Coating of titanium implants with BAG nanoparticles

Macroscopically, the whole implant surface was homogenously and uniformly covered with BAG coating, including the tips of implant threads **(Fig. 4)**.

Nano-roughness analysis

Table 1 shows the results of atomic force microscopy. Uncoated implants demonstrated an average surface nano-roughness of 0.51 nm, while BAG coated implants showed 0.46 nm. There was no statistically significant difference between them **(Fig. 5)**. The minor decrease in nano-roughness after BAG coating, accompanied with some surface planarization **(Fig. 6)**, indicates that the general uncoated substrate topography on the nanoscale has been maintained after coating.



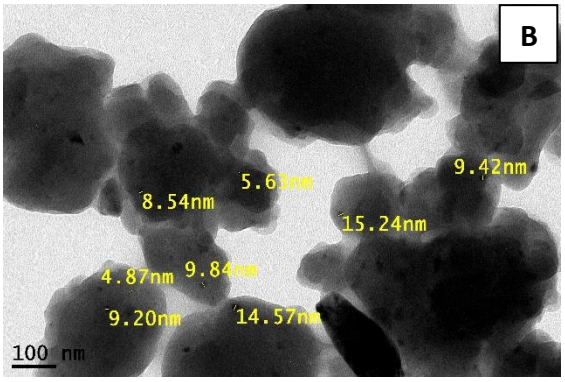


Figure 3: Transmission electron microscopy revealing particle size of less than 20 nm after introduction of BAG powder into planetary ball mill machine (A, scale bar = 200 nm and B, scale bar = 100 nm). Note high tendency of BAG for agglomeration.

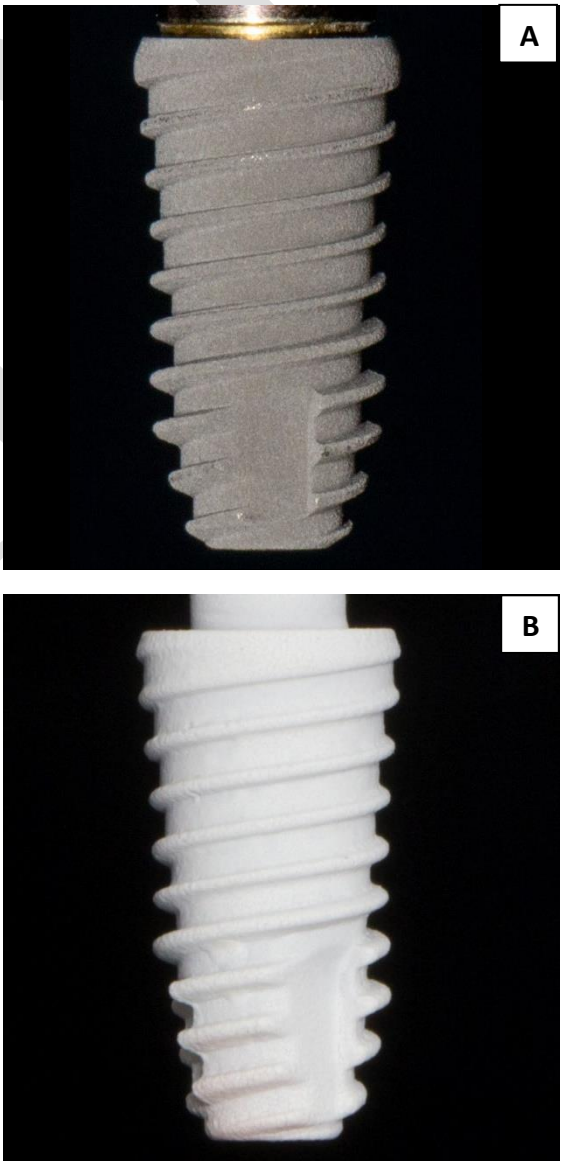


Figure 4: (A) Uncoated titanium implant. (B) Bioactive glass coated titanium implant.

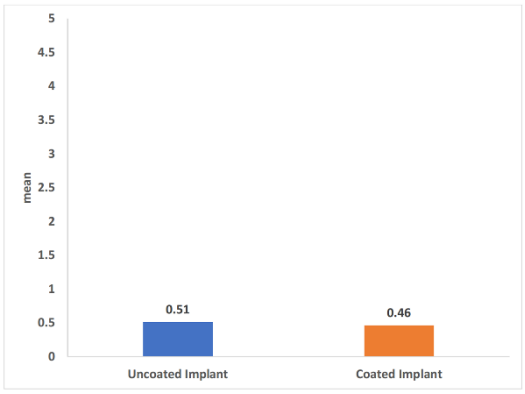
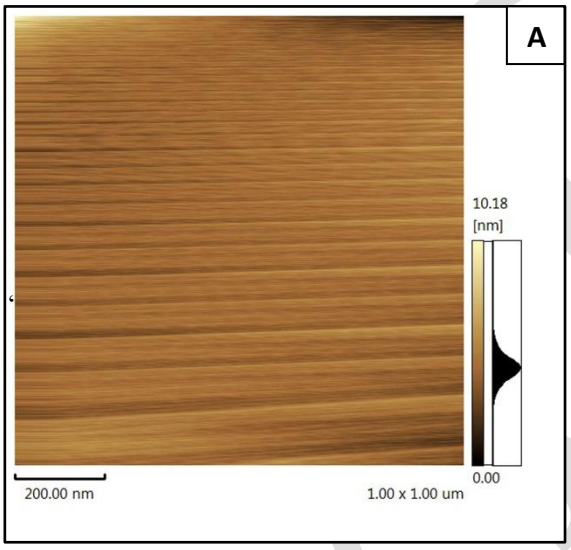
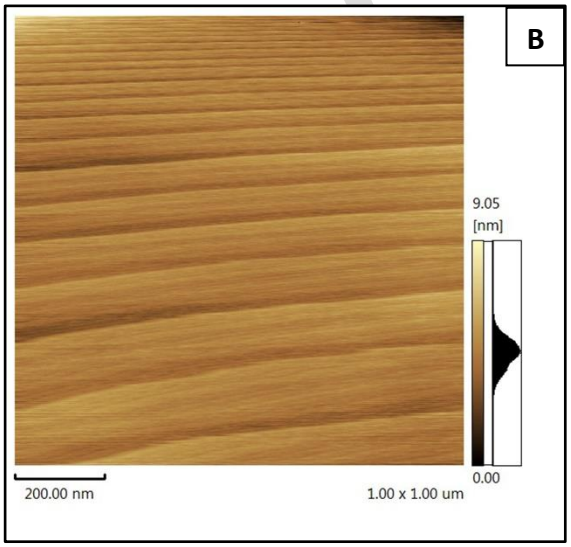
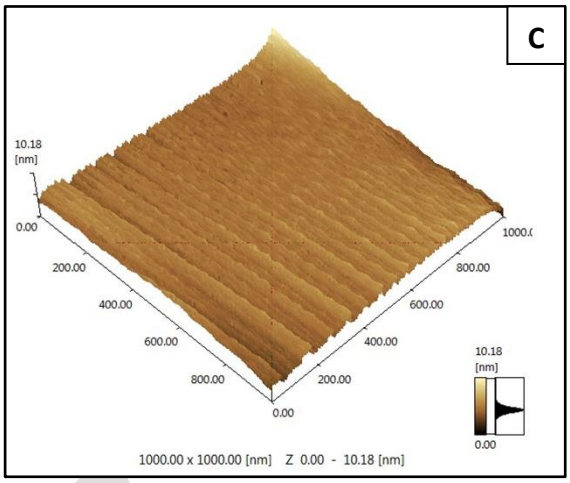


Figure 5: Difference between average surface nano-roughness of uncoated titanium implants (control group; n=10) and BAG coated titanium implants (test group; n=10) as measured via atomic force microscope.







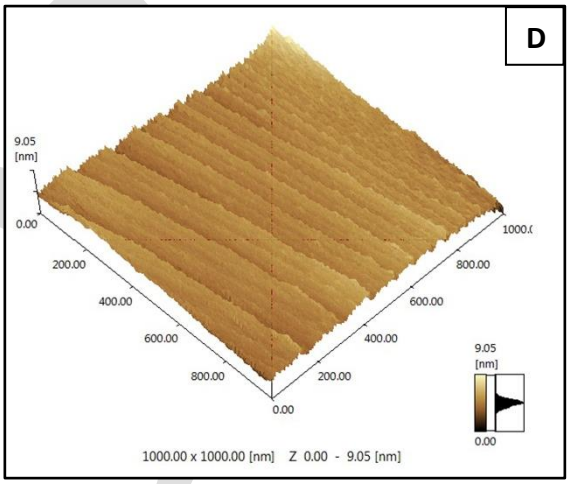


Figure 6: Atomic force microscopy scans comparing the nano-scale surface of uncoated and BAG coated titanium implants. Two-dimensional images of (A) Uncoated and (B) BAG coated implants. Three-dimensional images of (C) Uncoated and (D) BAG coated implants. The area of analysis used was 1 µm × 1 µm using non-contact dynamic mode.

Table (1): Comparison of average surface nano-roughness between uncoated and BAG coated titanium implants (nm) using Atomic Force Microscope

	Mean ± SD	*95% CI*
Uncoated implants	0.51 ± 0.15	0.34, 0.71
Coated implants	0.46 ± 0.12	0.28, 0.63
Mean difference	0.06 ± 0.21	-0.11, 0.22
Percent change	-3.43 ± 56.44	-73.50, 66.65
P value	0.45	

SD: Standard Deviation, CI: Confidence Interval
T-test was used

DISCUSSION

Dental implants have a high success rate in restoring lost teeth in healthy patients. However, failure may occur in medically compromised individuals and those with age-related problems, owing to poor-quality bone and delayed tissue healing, which makes dental implant therapy contraindicated.(28, 29) As a result, additional evidence-based research is needed for new implant surfaces that can integrate quickly and effectively into host bone tissue.(23) Bioactive glasses are gaining popularity due to their ability to bond to bone and soft tissues without being rejected. They are highly regarded for bone regeneration and repair, in addition to the capability of modifying their chemical composition to satisfy a variety of clinical applications and requirements.(30)

The aim of the present study was to develop a surface coating of 70S30C BAG nanoparticles on titanium dental implants, in order to improve cellular contact between the implant and host tissues, while also shortening the time required for early osseointegration. Titanium is bioinert and incapable of sustaining early implant fixation, particularly in patients with systemic diseases, resulting in decreased blood supply, disturbed bone reconstruction, and eventually implant failure.(31) This study employed titanium dental implants with a sandblasted, large grit, acid-etched (SLA) surface, where acid etching removes any residual air-abrasive particles, as reported by Kim et al.(32). In addition, Khalili and Naji(33) found that sandblasting followed by acid etching can improve mechanical adhesion between metal and coating.

According to Sarvanapavan and Hench(19), 70S30C BAG was chosen as the coating material because it is the most bioactive among the binary calcium silicate glass systems ($CaO\text{-}SiO_2$). The ability of this BAG to release ions, which govern a variety of physiological functions, has long been known. Silicon, located in active calcification sites in bones, has been found to have a role in osteoporosis regeneration and is a key element in management of bone metabolism. Calcium, on the other hand, increases osteoblast proliferation, differentiation, and extracellular matrix mineralization.(23) After BAG preparation, according to modified sol-gel protocol, it was subsequently milled into nanoparticles using ball milling technique. This economical milling process has been proven by Vafa et al.(24) and Ma et al.(34) to efficiently turn BAG particles into the nano-scale.. When compared to micro-scale particles, nanoparticles generate a more homogeneous coating and have higher bioactivity.(21, 22)

Many studies (25, 26, 35) have employed EPD with the implant functioning as the cathode and a metal cylinder acting as the anode to guarantee uniform coating all around the implant. After coating, implants were sintered since Braem et al.(25) found that sintered coatings had higher mechanical integrity and adherence to the substrate. To minimize oxidation, sintering was done in a vacuum furnace with argon.(25)

In order to get a combination of macro- and micro-roughness, and consequently enhance osseointegration, many companies roughen their implant surfaces by large grit sandblasting and acid etching (SLA), incorporating the benefits of each. The Straumann® SLA implant surface formed by a sand-blasting process, employing large-grit corundum particles (250 – 500 μm), followed by a few minutes of intense acid-etching with hydrochloric and sulfuric acids (HCl/H_2SO_4) at high temperature was the gold standard of this technology.(36) The results of atomic force microscopy showed no statistically significant difference in average surface roughness on the nano-scale between uncoated and BAG coated implants. However, they ensure that the deposited BAG layer is uniform such that it managed to coat the implant surface with minimal change to its topography, which is originally created by the manufacturer to improve osseointegration.(37, 38) One of the main characteristics of BAG is its gradual dissolution and becoming substituted by the developing bone tissue as the hydroxyapatite layer starts and continues to grow on its surface, hence exposing the original grit-blasted/acid-etched titanium implant surface to bone once BAG has performed its role in osseointegration.(39)

Patel et al.(20) tested nano-roughness for a surface coating of Chitosan (Chi) on titanium substrates by scanning probe microscope, before and after combining with different concentrations (0.25, 0.5, 0.75 mg/ml) of mesoporous BAG nanoparticles (MBGN). It was concluded that the average roughness (R_a) for Chi was the lowest (8.6070 ± 2.7825 nm) among other coatings, while the highest nano-roughness was observed for MBGN-0.5 coating (23.1785 ± 3.7263 nm). The results also indicated that nano-roughness increased with increasing MBGN concentration up to a limit, after which its concentration exceeds that of chitosan resulting in lower values of nano-roughness, due to formation of MBGN aggregates in the coating matrix.

Fares et al.(38) used AFM for scanning titanium disks before and after depositing silicon carbide (SiC) coating to assess its effect on final surface roughness. It was reported that despite the minor change in roughness after SiC deposition, the overall substrate topography was preserved.

Soltaninejad et al.(40) reported lower average surface roughness (30.34 ± 5.02 nm) for 45S5 BAG coated zirconia disks, when compared to sandblasted disks which showed higher roughness (163.10 ± 30.01 nm). However, the aim of their study was to test the micro-mechanical

interlocking of luting agents with zirconia substrates, not to deal with cells and osseointegration. The current study was limited by the investigation of complex shaped implants with irregular macro-topography, in contrast to flat substrates which are more easily scanned by atomic force microscope. Further investigations are required to test the durability of BAG coating upon in vitro insertion. Moreover, studies are needed to analyze the integration of BAG coated implants in vivo, together with their immunologic and biologic behavior.

CONCLUSION:

Within the limits of the current study, it can be concluded that employing EPD to coat titanium dental implants with sol-gel derived 70S30C BAG nanoparticles is a practical and cost-effective approach for surface coating. This technique with previously optimized parameters developed a homogeneous and uniform coating, showing surface planarization on the nanoscale, yet with no increase in average surface nano-roughness.

CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

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