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Original Article

Synthesis of Strontium Substituted Hydroxyapatite Coating on Titanium Via Hydrothermal Method

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Abstract: In this work, Strontium substituted hydroxyapatite (SrHA) coatings were successfully deposited onto etched titanium substrates in solutions of H_2SO_4 and HCl. The deposition was achieved by hydrothermal method by immersing the substrates in a solution containing $Ca(NO_3)_2.4H_2O$, $NH_4H_2PO_4$, and 5% $Sr(NO_3)_2$, followed by heating at 200°C for 12 hours. X-ray diffraction (XRD) analysis confirmed that all SrHA coatings exhibited a crystalline hydroxyapatite structure. Field-emission scanning electron microscopy (FE-SEM) revealed that the SrHA coatings exhibited microstructure. The reults of testing Bioactivity and in vitro biocompatibility of the SrHA-coated titanium substrates using SBF solution and baby hamster kidney (BHK) cells showed good biological properties of the SrHA coatings.

Keywords: Hydroxyapatite, Hydrothermal, Strontium substituted hydroxyapatite, Cell attachment, Implant.

1. Introduction

In recent years, advancements in biomaterials have played a pivotal role in the development of biomedical devices, especially in the field of orthopedics and dental implants [1]. Titanium (Ti),

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renowned for its good mechanical properties [2-4], high strength-to-weight ratio [3], good corrosion resistance [5], moderate biocompatibility [6]. Ti is a material of choice in biomedical implants because Ti is non-ferromagnetic and magnetic resonance imaging that can be performed on patients with titanium implant without risk [7]. However, challenges persist in optimizing the bioactivity of titanium implants to ensure successful osseointegration and long-term stability within the human body [8] as well as improving the corrosion resistance of the titanium [9, 10]. To address these issues, numerous research works have been done to improve the bioactivity of the titanium implants with surface modification being a key solution to overcome these problems [11-15].

Among the surface modification techniques with different coating layers, hydroxyapatite (HA), calcium phosphate compound has attracted interest due to its biocompatible and bioactive properties, making it be an ideal candidate for coating on implant surfaces [16-20]. Hydroxyapatite, with the general formula $Ca_5(PO_4)_3OH$ and unit cell formula $Ca_{10}(PO_4)_6(OH)_2$ [21] belongs to the family of calcium phosphate (CaP) ceramics with Ca/P molar ratio of 1.67, similar to that of natural bone and has favorable surface chemistry supporting bone development [9]. HA also acts as a protective coating for the titanium implants, improving the corrosion behavior of the implants which not only suppresses harmful ions that could be released from the surface of metallic implants but also extends their service life by preventing the failure of the implant that is being protected [22, 23]. Furthermore, the incorporation of strontium into hydroxyapatite introduces an intriguing dimension, as strontium has been reported to exhibit bone-stimulating effects and enhance osteogenic activity, therefore stimulating bone formation, growth, and healing [24-28]. Moreover, it is also reported that the incorporation of strontium increases the adhesion strength of the HA coating to the implants [29, 30].

In the pursuit of optimizing the biocompatibility of titanium implants, various coating methods have been explored to augment their interaction with the biological milieu such as physical vapor deposition [31, 32], sol-gel [33, 34], electrochemical deposition [35, 36], thermal spraying [37, 38] or hydrothermal [39-41]. Among the plethora of available methods, the hydrothermal approach emerges as a compelling choice for the deposition of strontium-substituted hydroxyapatite on titanium surfaces. The rationale behind this selection lies in the unique advantages offered by the hydrothermal method. Unlike other techniques, hydrothermal synthesis occurs under elevated temperatures and pressures in an aqueous environment, allowing for the precise control of particle size and crystallinity [42]. These factors are crucial in tailoring the coating to achieve optimal biological responses, ensuring a harmonious interface between the implant and the host tissue.

HA coatings on etched titanium substrates have been synthesized successfully as seen in previous work [43]. To expand this direction, we report the synthesis of SrHA coatings on the etched Ti substrates by the hydrothermal method. Therefore, the aim of this study is to investigate the SrHA films which have been successfully coated on titanium substrates, focusing on their surface morphology and biocompatibility.

2. Experiment Procedure

2.1. Preparing Titanium Surface with Etching Solution

Bare Ti plates with dimensions of $10\times10\times1$ mm^3 (Merck, 99.5%) were used for etched. Prior to acid etching, Ti substrates have been polished by 800 grits of SiC papers. The polished Ti substrates were cleaned in an ultrasonic bath for 10 min and dried in air. Then, the cleaned Ti sheets were immersed in a mixed solution of 48% H_2SO_4 (Merck, 98%) and 37% HCl (Merck, 37%) at 60 ^oC for 60 minutes. The etched Ti sheets were then rinsed with distilled water followed by alcohol and dried in air [44].

2.2. Creating Sr-doped HA Coating on the Surface of Etched Titanium

Solution "a" was obtained by completely dissolving 4.72 grams of $Ca(NO_3)_2.4H_2O$ (Merck, 99.5%) and 7.45 grams of $Na_2EDTA.2H_2O$ (Merck, 99%) in 35 ml of distilled water. Solution "b" was obtained by completely dissolving 1.4 grams of $NH_4H_2PO_4$ (Merck, 99%) in 35 ml of distilled water. Mixture of two solutions were then stirred continuously for about 30 minutes at room temperature. Finaly, 5% mol $Sr(NO_3)_2$ (Merck, 99%) denoted as 5SrHA were added into the mixture of solutions forstirring for 30 minutes.

The pH of the solution was adjusted to 9 by gradually adding NH_4OH (Merck, 35%) into the solution, followed by thorough stirring. Etched titanium sheets were placed into 100 ml teflon vessels positioned within stainless steel chamber. Within the teflon vessels, HA solutions supplemented with Sr^{2+} ions were added to facilitate the hydrothermal reaction. The hydrothermal synthesis process was conducted at 200 ^oC for 12 hours, followed by drying the samples at 60 ^oC for 1 hour. For comparative analysis, control samples, including non-etched titanium samples, were also synthesized with Sr^{2+} supplemented HA.

2.3. Surface Characterization and Biocompatibility Assessment

X-ray diffraction (XRD, D8 Advance, Bruker, Germany) was carried-out to characterize the crystalline structures of the samples, using Cu-Kα radiation (λ = 1.54056 nm). The morphology of 5SrHA was studied using digital optical microscopy (VHX-7000). Field emission scanning electron microscopy (FE-SEM, JEOL JSM-7600F device (Japan) was used to observe the surface morphology of SrHA. The bioactivity of the 5SrHA was evaluated using simulated body fluid (SBF) model. The 5SrHA was immersed in the SBF solution and then placed in the furnace at a temperature of 37 °C for 7 days. The specimens were then washed three times using ethanol followed by drying at 37 °C for 1 h. The formation of the bone mineral layer on the SrHA was examined using FE-SEM. Prior to test in vitro cells, the titanium substrate and SrHA coating were sterilized by autoclaving at 121^oC for. Baby hamster kidney (*BHK cells*) was maintained in DMEM at 37 ^oC in humidified air and 5% CO_2. Cell suspensions density of 2×10^4 cell/ml were then seeded on the Ti and 5SrHA coating. Cell attachment was observed by confocal laser scanning microscopy (FV3000, Olympus, Japan). After culturing for 72 h, the BHK cells on the 5SrHA coating and the Ti were fixed in 4% paraformaldehyde in PBS for 10 min, washed in PBS, permeabilized with 0.1% Triton X-100 in PBS for 5 min, washed in PBS and stained with fluorescent phalloidin for 45 min. The BHK cell nuclei were labelled with DAPI for 5 min. The stained BHK cells attached on the samples were placed on a glass cover slide, and the cell attachment was observed.

3. Results and Discussion

3.1. Surface Characteristics

In Fig. 1, SEM images depict the morphology of HA (Fig. 1a) and 5SrHA (Fig. 1b). It is observed that in the absence of Sr, the hexagonal rod-like structure of HA is clearly observed on the surface of etched titanium sheet. The length of the rods was of approximately 110 μm.

In Fig. 2a, the FE-SEM image reveals a hexagonal diameter of approximately 4 μm. Several studies have indicated that as the concentration of Sr^{2+} ions increases in the HA synthesis solution, the size of the HA tubes decreases [24-26, 45]. In Fig. 1b, the size of the 5SrHA tubes is not clearly observed, suggesting a structural change in the tubes due to the substitution of Sr^{2+} for Ca^{2+} [45]. The rod-like

structure of the material layer on the 5SrHA sample (Fig. 2b) and the lenght of the 5SrHA rods is of approximately 500 nm, representing a reduction by 21 times compared to the hexagonal rod-like HA (Fig. 1a), with a proportional decrease in the diameter of the 5SrHA rods.

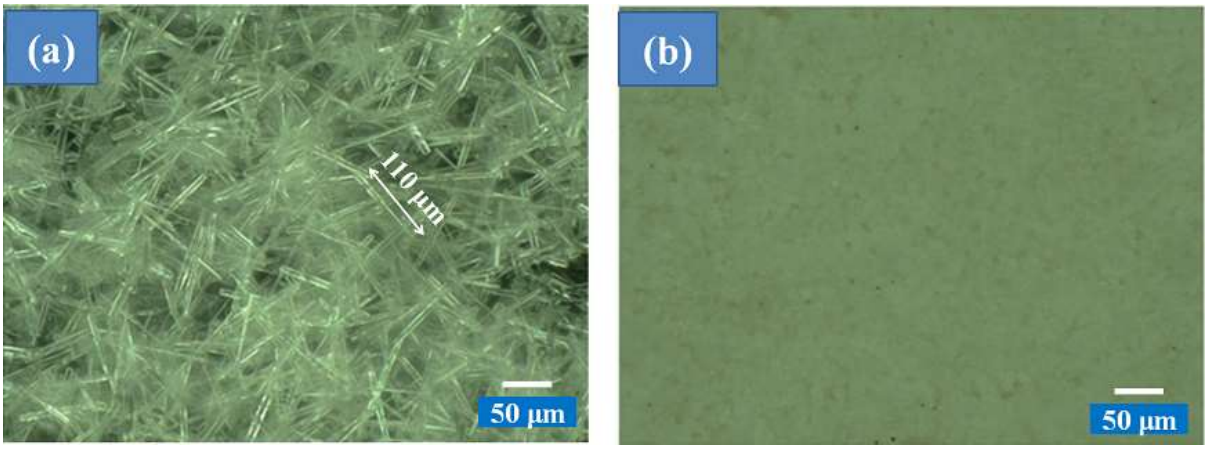

Figure 1. Digital optical image of the (a) HA coating and (b) 5SrHA on the etched titanium substrate.

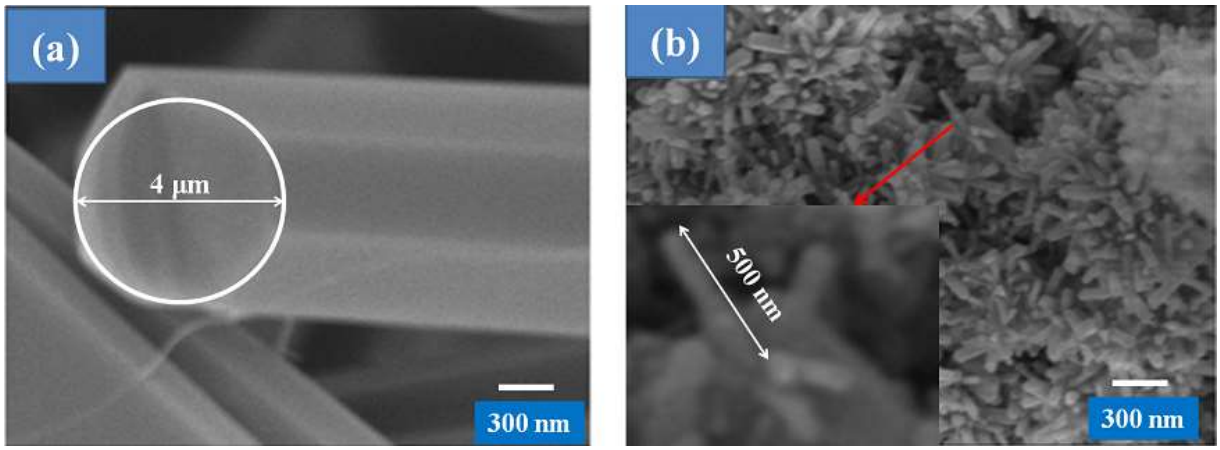

Figure 2. FE-SEM images of (a) HA and (b) 5SrHA coating on etched Ti substrate.

3.2 Chemical Composition Analysis

Fig. 3 illustrates the X-ray diffraction patterns of two types of coatings: HA (Fig. 3a) and 5SrHA (Fig. 3b) deposited on etched titanium sheets. Interestingly, there is no noticeable difference in the XRD peak positions between Fig. 3a and Fig. 3b. This can be explained by the nature of pure HA, which is known to exist as the compound $Ca_{10}(PO_4)_6(OH)_2$ according to the standard reference JCPDS 09-0432. When Sr^{2+} replaces Ca^{2+} in this compound, it forms $Ca_{10-x}Sr_x(PO_4)_6(OH)_2$, where x ranges from 0 to 10. This new compound maintains a hexagonal structure similar to $Ca_{10}(PO_4)_6(OH)_2$. Additionally, since the ionic radii of Sr^{2+} and Ca^{2+} ions are quite similar, there is no significant peak shifting observed in Fig. 3. Consequently, there is no need to mark the positions of each compound in the X-ray diffraction patterns of the HA and 5SrHA samples.

Fig. 4 shows the EDS image of the 5SrHA sample regarding its chemical composition and the content of elements on the surface of the 5SrHA sample. The Sr content in the 5SrHA sample is relatively large at 16.3% by weight, resulting in a Sr/(Sr+Ca) ratio of 0.38. This explains the relatively high substitution of Sr^{2+} for Ca^{2+}.

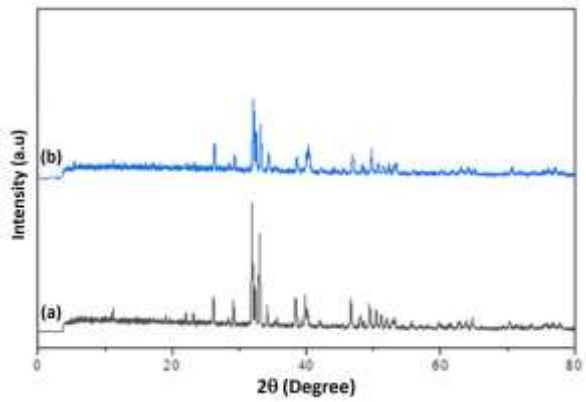

Figure 3. XRD pattern (a) HA and (b) 5SrHA coating on the etched titanium.

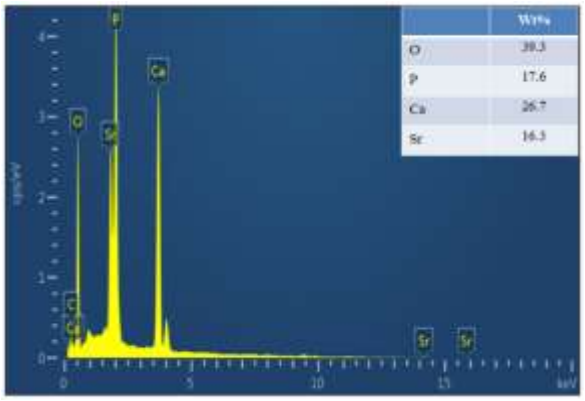

Figure 4. EDS of 5SrHA coating on the etched titanium.

3.3. Bioactivity of 5SrHA Coating on Titanium

Fig. 5 illustrates FE-SEM images of apatite minerals formed outside the 5SrHA crystals by immersing the 5SrHA sample in SBF solution at 37 °C for 7 days. These new bone minerals cover the surface of the rod-like HA crystals, altering their morphology. This demonstrates that the 5SrHA coating on titanium subjected to etching exhibits relatively good biological activity, facilitating the exchange of materials with the living environment, and resulting in the formation of a bonded bone mineral layer.

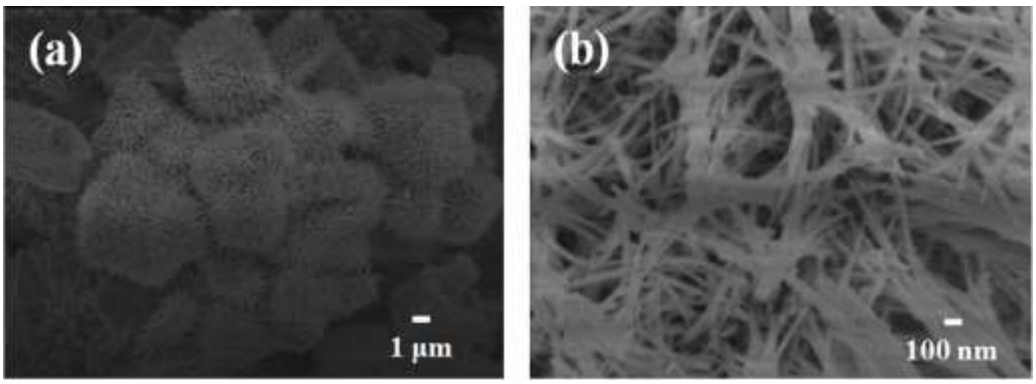

Figure 5. FE-SEM images showing the bioactivity of 5SrHA coating on etched titanium immersion in SBF for 7 days with (a) 3k and (b) 40k magnification.

3.4 Biological Compatibility Testing

Fig. 6 depicts confocal laser scanning microscope (CLSM) images of BHK cell attachment on both Ti and 5SrHA coatings after 72 hours of culturing. As described in Fig. 6, cells on Ti and SrHA exhibit

normal fibroblastic cell morphology, with clear nuclei and cell membranes. However, the cell density on SrHA is significantly higher than that on Ti. This indicates that the SrHA coating on etched titanium is a biocompatible coating layer after hydrothermal processing, with potential for further investigation in implant materials.

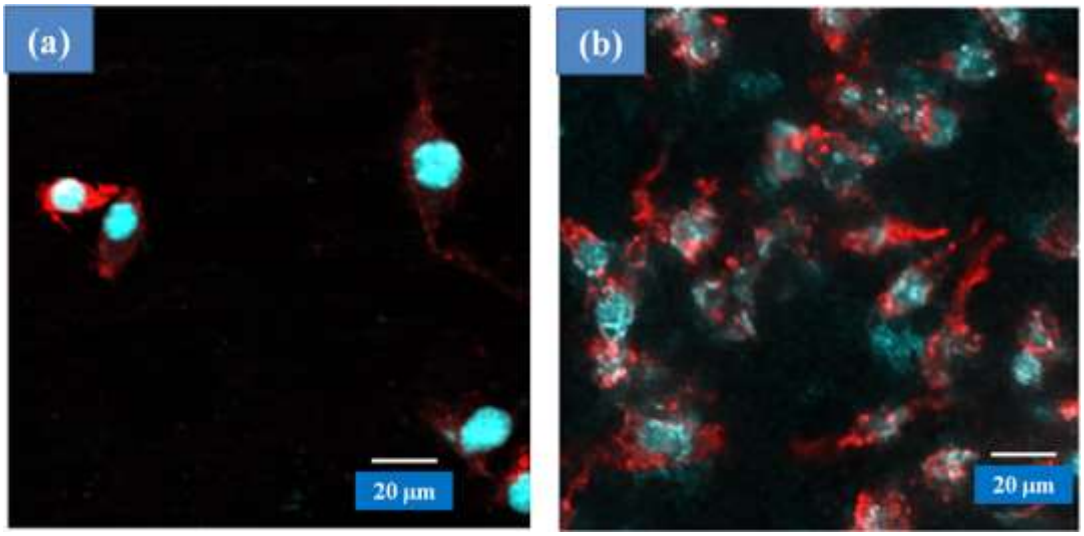

Figure 6. CLSM image showing the biocompatility of samples coating on etched titanium (a) Ti; (b) 5SrHA.

4. Conclusion

In this work, 5SrHA samples were successfully deposited onto etched Ti substrates by hydrothermal method. The HA coating exhibited a rod-like hexagonal morphology. Substituting Ca^{2+} with Sr^{2+} from $Sr(NO_3)_2$ solution in the HA crystal structure significantly reduced the dimensions of the SrHA structure, with a relatively high Sr content, and the Sr/(Sr+Ca) ratio was of 0.38. The 5SrHA coating was evaluated for its interaction with simulated body fluid (SBF) after 7 days, demonstrating good biological compatibility as evidenced by BHK cell attachment after 72 hours.

Acknowledgments

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