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Research Article

Porous Titanium Scaffold: A New Design for Controlled Drug Delivery

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Gelatin crosslinking using conventional methods is usually associated with some toxic side effects. In this research, therefore, the vacuum heating method at 10 Pascal and 140°C under different times of 8, 16, and 32 h was used to cross-link strontium-loaded gelatin microparticles with varying degrees obtained by the oil/water mixing method on titanium scaffolds by the dip-coating method to avoid toxicity and also to control the strontium release rate to the surrounding tissue. The possible phases formed on the surface of the porous titanium scaffolds, the gelatin microparticle distribution, gelatin strontium loading, and strontium release were characterized using thin film X-ray diffraction, Fourier transform infrared spectroscopy, scanning electron microscopy (SEM), and inductively coupled plasma-mass spectrometer (ICP-MS) machines, respectively. The results indicated that at 600°C, the rutile phase was formed on the surface of the heat-treated titanium scaffolds. Furthermore, strontium was successfully loaded in the spherical gelatin microparticles, and the strontium-loaded gelatin microparticles were distributed uniformly on the surface of the titanium scaffolds, while the rate of the *in vitro* strontium release decreased by increasing the time of the gelatin microparticle vacuum-heat crosslinking, whereas at the burst release step, the *in vitro* strontium release rates were around 5, 4.4, and 2.5 ppm/h, for the 8, 16, and 32 h vacuum-heat cross-linked gelatin microparticles, respectively.

1. Introduction

One of the most effective methods in hard tissue engineering is the development of a biocompatible scaffold with interconnected porosity which can provide suitable mechanical properties, nutrient delivery, waste removal, cell attachment/viability, osteoconductivity, and bone ingrowth ability [1–5].

As a bioinert material, titanium is one of the most widely used metals in dental/bone implantation due to its high strength/weight ratio, good biocompatibility, and nonallergic effect [6–9]. Many surface treatment methods have been introduced by researchers to alleviate the bioinertness of titanium, including direct oxidation which is an effective method for improving the bonding ability of titanium implant to the surrounding bone [3]. In this method due to the high temperature, titanium reacts with the oxygen present in the surrounding air resulting in the formation of titanium oxide (rutile) at the surface [10–13].

Apart from the surface-modified and bioactivated titanium, localized drug or ion release is also advantageous, and its controlled release can catalyze bone healing or inhibit infection or disease after implantation [14–16]. Since the surface of the titanium cannot release drug/ion, a well-designed combination of a metal-biodegradable ceramic or metal-biodegradable polymer must be used for tooth-/bone-healing purposes.

Superior properties of gelatin such as rapid and controllable biodegradability, biocompatibility, and ease of processing have resulted in the immense use of gelatin in medical applications and drug delivery systems [17]. By crosslinking the gelatin, its degradation rate reduces and can be matched to the requirements of the surrounding tissue [18].

Glutaraldehyde solution is a well-known agent for gelatin crosslinking. While glutaraldehyde residue is toxic to the alive surrounding tissues, vacuum heating as a clean method can be used for gelatin crosslinking [19]. However, the decomposition or deterioration of drugs at high temperatures has restricted this method for crosslinking drug-loaded gelatin.

One of the most important ions for bone healing is strontium. The dual action of strontium ion makes it a beneficial drug for bone treatment, and it is a useful agent for osteoporosis [20]. The simultaneous dual action of strontium includes increasing bone formation rate by the positive stimulation of osteoblast cells and also reducing bone resorption rate by the negative stimulation of osteoclast cells [20]. Regarding the side effects of strontium [21], localized strontium release with a controlled rate could improve bone formation and mineral density (BMD) in patients.

Systematic or uncontrolled drug or ion release with disconformity to the surrounding tissue requirements is still controversial [22]. Biodegradable ceramics or polymers are widely suggested candidates for load-bearing scaffolds which have a drug-release ability. However, the higher mechanical properties of metals compared to polymers and ceramics make them a more reliable choice for hard tissue implantations exposed to mechanical loading [23]. Therefore, a novel design of metal-biopolymer seems to be necessary for optimized and accelerated bone healing using scaffold implantation.

The novelty of this study is attributed to the use of gelatin microparticles as a controlled release system for strontium ions on the surface of porous Ti scaffolds. The study presents a new model for the controlled release of strontium ions, which has not been reported before. Additionally, the effects of different vacuum heating times on the degree of crosslinking and the strontium release rate were investigated, which provides new insights into the optimization of strontium ion release from gelatin microparticles on Ti scaffolds. Therefore, the study contributes to the development of more effective and controlled release systems for strontium ions for potential use in orthopedic implant applications.

2. Materials and Methods

2.1. Fabrication of Surface Bioactivated Titanium Scaffolds. The powder metallurgy-space holder method was utilized to prepare disc-shaped porous titanium scaffolds with a nominal porosity of 70 vol.% (diameter of 13 mm and height of 2 mm), as previously described [24]. Subsequently, titanium scaffolds were heated at 600°C for 240 min in an atmospheric furnace using a heating/cooling rate of 5°C/min [13].

2.2. Fabrication of Strontium Ion-Loaded Gelatin Microparticles. The oil/water mixing method was used to synthesize gelatin microparticles containing strontium ion ($Sr(OH)_2$), as previously described [25]. For crosslinking gelatin at different degrees, the coated titanium scaffolds with strontium-loaded gelatin microparticles were heated at 140°C, at a vacuum level of 10 Pascal for 8, 16, and 32 h.

2.3. Microscopic Observation. Scanning electron microscopy (SEM: JCM-6000 Plus, JEOL, Japan) was used for surface morphology observation of the surface-treated titanium scaffolds and the distribution of gelatin microparticles on the titanium scaffolds. To inhibit electron discharge during SEM observation, a thin layer of gold was deposited on the surface of the samples using a sputtering system.

2.4. Phase Identification. A thin film X-ray diffraction (TF-XRD) system was utilized for possible phase formation on the surface of the bioactivated porous titanium scaffolds. The TF-XRD measurements were done using a Cu-Kα X-ray lamp at 40 kV and 40 mA and a glancing angle of 1° against the incident beam.

2.5. Structural Analysis. The chemical structures of gelatin microparticles, strontium hydroxide, and strontium-loaded gelatin microparticles were studied using Fourier transform infrared spectroscopy (FTIR: SHIMADZU, 8400S, Japan) in a KBr matrix.

2.6. In Vitro Strontium Release Assessment. Each of the microparticle-deposited titanium scaffolds was soaked in 15 ml of phosphate-buffered solution (PBS) at 37°C for designated time points of 1, 2, 4, 8, 16, 32, and 64 h. The PBS was poured out from the test tube at each time point, and the concentration of the released strontium ion in the PBS was measured using an inductively coupled plasma-mass spectrometer (ICP-MS: HITACHI, PS7800). The test and measurement process was repeated three times for each sample, after which 15 ml of fresh PBS was added to the test tube. The resulting cumulative strontium ion concentrations were then plotted versus the soaking time.

3. Results and Discussion

3.1. Surface Morphology. The SEM micrographs of the titanium scaffold and microparticle-deposited titanium scaffolds are presented in Figure 1. According to Figure 1(a), both micropores (smaller than 10 μm) and macrointerconnected pores (the size of about 350 μm) exist in the matrix of the titanium scaffold which can facilitate nutrition and drug delivery around the titanium implant. Regarding the mean diameter of the microparticles (smaller than 20 micrometers) and the interconnectivity of the macropores of the titanium scaffolds [25], microparticles could diffuse into the inner macropores of the titanium scaffold. According to Figure 1(b), gelatin microparticles were successfully and homogenously deposited on the whole surface of the titanium scaffold struts.

The good distribution of strontium-loaded gelatin microparticles on all the titanium scaffold surfaces could inhibit localized or concentrated strontium release to the surrounding tissue.

3.2. Phase Identification. The phase formation due to the surface treatment of titanium scaffolds was investigated using thin film X-ray diffraction. Figure 2 presents the X-ray diffraction pattern of the as-sintered and surface-treated titanium scaffolds. The as-sintered titanium scaffolds

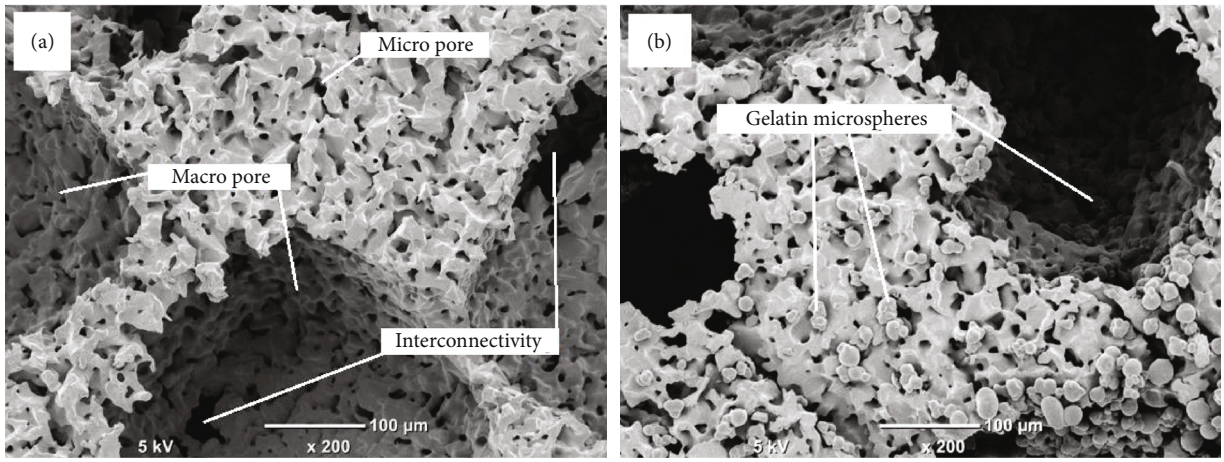

Figure 1: SEM images of the titanium scaffold: (a) before microparticle deposition and (b) after microparticle deposition.

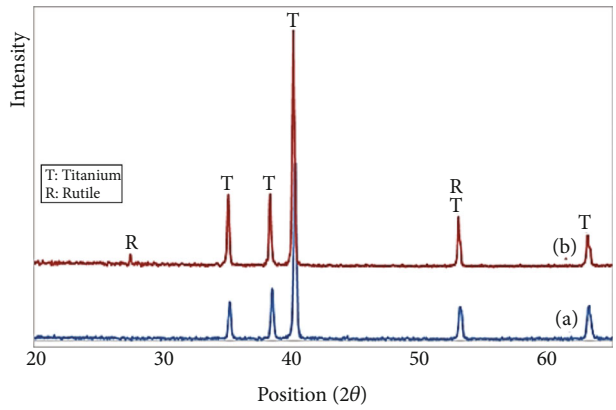

Figure 2: X-ray diffraction pattern of the: (a) as-sintered and (b) surface-treated titanium scaffolds after heat treatment at 600°C.

showed peaks related to pure titanium, while the surface-treated sample presented peaks related to pure titanium and rutile phase. Therefore, it seems that the titanium scaffold has been covered by a thin layer of rutile titania (TiO_2) due to the surface treatment. Both anatase and rutile (two different crystal structures of titania) phases are bioactive and can improve the bone-bonding ability of the titanium scaffolds [26].

3.3. Structural Properties. FTIR spectra of the gelatin microparticles, strontium hydroxide, and strontium-loaded gelatin microparticles are shown in Figure 3. According to Figure 3(a), the FTIR spectrum of the cross-linked gelatin microparticles without strontium loading exhibited major peaks at 1645, 1542, and 1238 cm^{-1} correspondence to amide I, amide II, and amide III groups, respectively. According to Figures 3(a) and 3(b), a peak at 3490 cm^{-1} is replicated on the spectrum of the strontium-loaded gelatin microparticles, indicating that the strontium was successfully loaded on the gelatin microparticles. According to Figure 3(c), the FTIR spectrum of the strontium hydroxide exhibited a peak at 3490 cm^{-1} which is in correspondence to the OH^- stretching mode of strontium hydroxide [25].

3.4. In Vitro Strontium Release. To adjust the strontium release rate, different degrees of gelatin crosslinking were used. The strontium release profile was obtained by measuring its soaking concentration in PBS vs. time. The cumulative concentration of the released strontium to the surrounding PBS is presented in Figure 4. According to the strontium release profile, by increasing the time of the vacuum-heat crosslinking of the gelatin microparticles, the release rate of strontium decreased. Therefore, it seems that the strontium release rate could be adjusted according to the requirements of the surrounding tissues by controlling the time of the gelatin vacuum-heat crosslinking. According to Figure 4, the curve of the ion release consists of two steps: the burst release of strontium at the initial times of soaking and subsequently the slow release of strontium to the surrounding PBS. The slope of the diagram indicates that with the increase in the time of the vacuum-heat crosslinking of gelatin, the degradation rate of gelatin and the rate of strontium release decreased.

According to Figure 4, the burst release of strontium was prolonged for about 30 hours, and after that, its release significantly decreased. At the burst release step, the *in vitro* strontium release rates were about 5, 4.4, and 2.5 ppm/h, for the 8, 16, and 32 h vacuum-heat cross-linked gelatin microparticles, respectively.

The drug release profile (shown in Figure 4) was similar to the findings reported by Mosallanezhad et al. [27]. Therefore, the Peppas model ($M_t/M_\infty = Kt^n$) was employed for curve fitting and to investigate the kinetics of drug release [27]. The results obtained from the Peppas model are presented in Figure 4 using dashed lines. It can be observed that the Peppas model provided a good fit to the experimental data, particularly for the 32-hour cross-linked sample. The correlation coefficients (R^2) for the Peppas model were 0.87, 0.96, and 0.98 for the 8-hour, 16-hour, and 32-hour cross-linked samples, respectively. Moreover, the exponent (n) values for the Peppas model were 0.496, 0.577, and

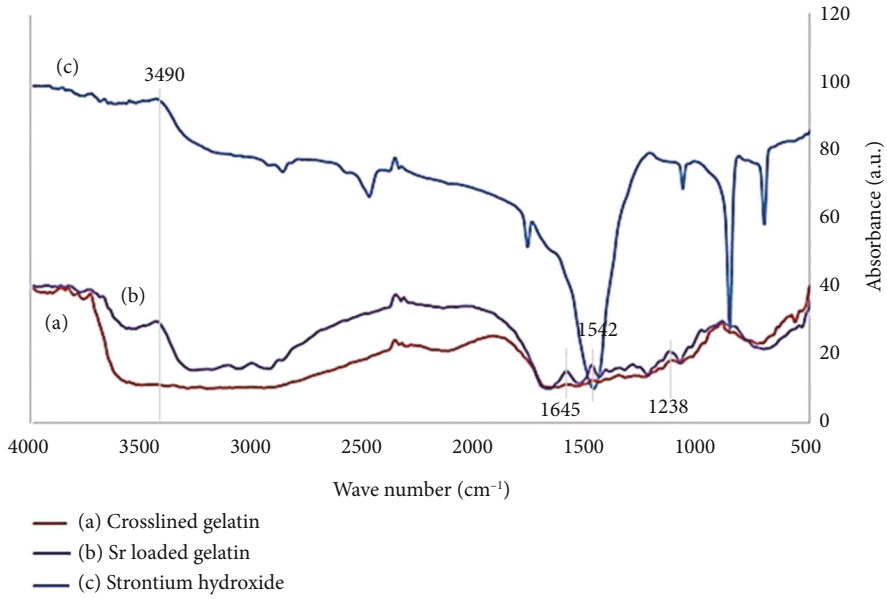

Figure 3: FTIR spectra of (a) gelatin microparticles, (b) strontium-loaded gelatin microparticles, and (c) strontium hydroxide.

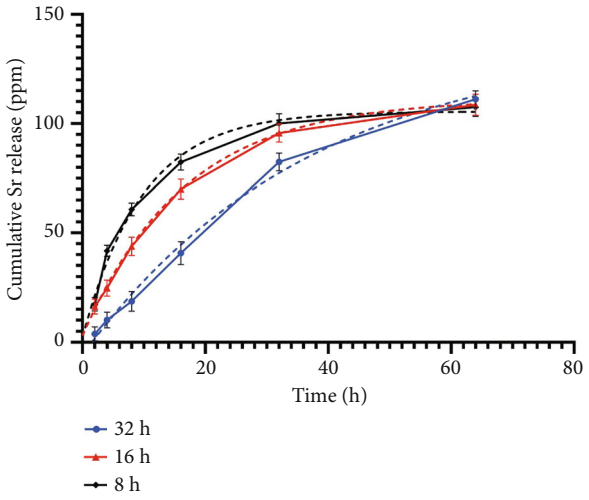

Figure 4: Profile of *in vitro* strontium release from vacuum-heated strontium-loaded gelatin into the PBS, dash lines present the fitted models.

0.989 for the 8-hour, 16-hour, and 32-hour cross-linked samples, respectively, indicating that all samples had a non-Fickian profile of strontium release.

As described by Ozeki and Tabata, there was a good correlation between the degradation rate of gelatin and its number of cross-links, and the degradability of gelatin is controlled by the number of cross-links [28]. The ratio of cross-links/gelatin molecule increased with increasing the time of the vacuum-heat crosslinking. Furthermore, vacuum heating generated the chemical bonding between the carboxyl groups and amino groups of gelatin molecules due to dehydration [28].

Comparing the results of this study to those obtained in other research using bioceramics for targeted or controlled drug release indicated that the degradation rate of bioceramics is slower than biopolymers [29]. According to the clinical requirements, biodegradable polymers and ceramics could be used for short-term and long-term drug release, respectively.

4. Conclusion

To improve the biofunctionalization of titanium scaffolds, two different surface treatments were used: (a) air heating of titanium and (b) deposition of strontium ion-loaded gelatin microparticles. The air heating of titanium will result in rutile formation at the surface of titanium, while the deposition of strontium ion-loaded gelatin microparticles was used with different degrees of crosslinking on the surface of the treated titanium scaffolds for the controlled release rate of strontium and improvement of the bone formation rate around the implanted scaffolds. At the burst release step, by increasing the time of the vacuum-heat crosslinking of gelatin microparticles from 8 to 32 h, the *in vitro* strontium release rate decreased from about 5 to 2.5 ppm/h, respectively. Furthermore, the Peppas model ($M_t/M_\infty = Kt^n$) was used for curve fitting and to investigate the kinetics of drug release which showed good fitting with the experimental results and also that all the samples had the non-Fickian profile of strontium release.

Data Availability

The data that support the findings of this study are not openly available due to the university laws but are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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