Research Article

Visible Light Irradiation-Mediated Drug Elution Activity of Nitrogen-Doped TiO₂ Nanotubes

Seunghan Oh,¹ Kyung-Suk Moon,¹ Joo-Hee Moon,² Ji-Myung Bae,¹ and Sungho Jin³

¹Department of Dental Biomaterials and Institute of Biomaterial and Implant, College of Dentistry, Wonkwang University, Iksan, Jeonbuk 570-749, Republic of Korea
²Department of Dentistry, College of Dentistry, Wonkwang University, Iksan, Jeonbuk 570-749, Republic of Korea
³Department of Mechanical and Aerospace Engineering, University of California, San Diego, La Jolla, CA 92093, USA

Correspondence should be addressed to Seunghan Oh; shoh@wkku.ac.kr and Sungho Jin; jin@ucsd.edu

Received 19 October 2012; Revised 23 December 2012; Accepted 24 December 2012

Academic Editor: Fengqiang Sun

Copyright © 2013 Seunghan Oh et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We have developed nitrogen-doped TiO₂ nanotubes showing photocatalytic activity in the visible light region and have investigated the triggered release of antibiotics from these nanotubes in response to remote visible light irradiation. Scanning electron microscopy (SEM) observations indicated that the structure of TiO₂ nanotubes was not destroyed on the conditions of 0.05 and 0.1M diethanolamine treatment. The results of X-ray photoelectron spectroscopy (XPS) confirmed that nitrogen, in the forms of nitrite (NO₂⁻) and nitrogen monoxide (NO), had been incorporated into the TiO₂ nanotube surface. A drug-release test revealed that the antibiotic-loaded TiO₂ nanotubes showed sustained and prolonged drug elution with the help of polylactic acid. Visible light irradiation tests showed that the antibiotic release from nitrogen-doped TiO₂ nanotubes was significantly higher than that from pure TiO₂ nanotubes (P < 0.05).

1. Introduction

Development of TiO₂ nanostructures has been a focus area in the fields of photocatalysis [1–3], solar cells [4], and biomedical applications [5–7]. TiO₂ is well known as a highly efficient photocatalyst and has been widely used for degrading organic pollutants for air purification and sterilization [8, 9]. However, the band gap of TiO₂ allows limited photocatalytic activity, which occurs solely in the narrow ranges of ultraviolet light. Many researchers have tried to develop visible light photocatalysts by modifying the structure of titanium dioxide. Metal doping is one of the typical modifications of TiO₂, and several kinds of metal elements, such as Cr, Co, Mo, Mn, and V, have been used to adjust the band gap of TiO₂ and promote its photocatalytic activity in the visible light range.

The unique advantages of TiO₂ nanostructures on Ti over microscale TiO₂ structures have been reported in the field of solar cells and biomaterials [10–15]. In addition, the morphology and crystallinity of TiO₂ nanotubes affect the adhesion, proliferation, and functionality of many types of cells [16–19]. For example, it is known that an array of TiO₂ nanotubes on Ti promotes osseointegration into animal bone in vivo [14, 20, 21].

Bacterial infection is one of the major reasons for the failure of orthopedic implants. An ideal solution to reduce bacterial infection is antibiotic drug therapy around 2 months after implant surgery. The delivery methods of antibiotics are generally systemic, intravenous, intramuscular, and topical. However, systemic antibiotic delivery is typically associated with certain side effects, including unwanted cytotoxicity. In recent years, various drug-delivery systems have been developed to facilitate drug effectiveness at the site of implantation [22, 23]. These drug-delivery devices release a proper dose of the drug at the site of action and thereby avoid undesirable side effects. However, these devices lack the ability to exert an on-off control over drug release. Consideration of release periods as well as the elution point of drugs is very important to reduce bacterial infection. Unwanted high doses of the drug lead to unavoidable toxic effects. Being able to trigger
the antibiotic release, for example, by using light stimulation, would be highly desirable to minimize complications and side effects for the orthopaedic implants. However, ultra violet (UV) light triggering TiO₂ photocatalytic activity is well known to be used for sterilization and to be harmful to mucous membrane in mouth. Therefore, the development of new TiO₂ showing photocatalytic activity at visible light region is required to minimize the side effect of UV light irradiation and promote the effect of remote-controlled drug release. In terms of the photocatalytic activity of TiO₂ nanotubes at visible light region, several studies reported that nitrogen or Fe-doped TiO₂ nanotubes showed excellent photocatalytic activity and degree of dye degradation compared to pure TiO₂ nanotubes by visible light irradiation [24–27].

In this study, we developed nitrogen-doped 100 nm TiO₂ nanotubes on Ti, performed surface analysis to examine the amounts and structure of nitrogen incorporated into Ti, and investigated the triggered release of antibiotic drug from nitrogen-doped TiO₂ nanotubes in response to remote visible light irradiation.

2. Materials and Methods

2.1. Fabrication of Nitrogen-Doped TiO₂ Nanotubes. As reported previously [28], a machined Ti sheet (0.2 mm thick, 99.5%; Hyundai Titanium Co., Republic of Korea) was electropolished by an electrochemical etching process and cleaned with acetone and deionized water. To prepare nitrogen-doped TiO₂ nanotube arrays on a Ti sheet, 0.05, 0.1, or 0.2 M diethanolamine (DEA; Sigma, MO, USA) was added into 0.5 w/v% hydrofluoric acid (48 w/v%; Merck, NJ, USA) in a mixture of water and acetic acid (98 w/v%; JT Baker, NJ, USA) in the volumetric ratio of 7:1. Anodization voltage and time were 20 V and 30 min, respectively.

Samples were then rinsed with deionized water, dried at 60°C for 24 h, and heat treated at 500°C for 2 h in an atmosphere of N₂. Morphological and surface analyses of nitrogen-doped TiO₂ nanotube arrays were performed by field emission scanning electron microscopy (FE-SEM, S4800; Hitachi/Horiba, Japan), transmission electron microscopy (TEM, Tecnai G2; FEI Co., USA, power: 300 kV), and X-ray photoelectron spectroscopy (XPS, K-Alpha ESKA system; Thermo, USA), respectively. Also, contact angle of experimental specimen was measured by contact angle meter ( Theta Optical Tensiometer, KSV, Finland). The solvent of contact angle measurement was D.I. water.

2.2. Drug Release Test. Three antibacterial drugs, tetracycline (Sigma, MO, USA), cetylpyridinium chloride (CPC; Sigma, MO, USA), and chlorhexidine (Sigma, MO, USA), were mixed with polyactic acid (PLA; Sigma, MO, USA) and loaded into TiO₂ nanotubes. Tetracycline is an antibiotic drug that serves as a protein synthesis inhibitor. Chlorhexidine is a chemical antiseptic, while cetylpyridinium chloride is a strong bactericide. The amount of antibiotics released as a function of incubation time was measured by a microplate ELISA reader (Spectra Max 250; Thermo Electron Co., USA).

The amount of antibiotics released in response to visible right irradiation was also measured by the microplate ELISA reader. The source of visible light was a dental light curing unit (intensity, 1000 mW/cm²; wavenumber of irradiated light, 470 nm; Elipar Free-Light 2; 3 M ESPE Co., USA).

2.3. Data Analysis. All data were expressed as mean ± standard deviation values and analyzed statistically by one-way ANOVA (SPSS 12.0; SPSS GmbH, Germany) and post hoc Duncan’s multiple range test. Significant differences were considered if P values were less than 0.05.

3. Results and Discussion

As shown in Figures 1(a), 1(b), and 1(c), SEM images show the differences in appearance among N-doped 100 nm TiO₂ nanotubes with 0.05 M, 0.1 M, and 0.2 M of DEA. The micrographs of N-doped TiO₂ nanotubes show somewhat randomly organized nanotube geometry with different concentrations of DEA, in contrast to the SEM image of undoped TiO₂ nanotubes. However, the nanotubular structure was not formed on the Ti surface at a DEA concentration of 0.2 M. Therefore, we examined the characteristics of N-doped TiO₂ nanotubes at a DEA concentration of 0.1 M. TEM image (Figure 1(d)) of N-doped 100 nm TiO₂ nanotubes treated by 0.1 M DEA indicates that nanosized (100 nm thickness) porous layer was formed at top surface of TiO₂ nanotubes. High-magnification TEM image (Figure 1(e)) illustrates that the lattice spacing of newly formed layer is 0.35 nm, and this spacing is corresponding to the (101) planes of anatase TiO₂ as previously reported [29].

Figure 2 indicates X-ray diffraction (XRD) patterns of undoped and N-doped TiO₂ nanotubes. As shown, XRD mainly detected anatase TiO₂ and Ti crystalline phases. There was no dramatic difference in crystallinity between undoped and N-doped TiO₂ nanotubes after heat treatment. Therefore, we expect that DEA treatment had essentially no effect on the crystallinity of TiO₂ nanotubes in this study.

The XPS spectra of TiO₂ nanotubes and N-doped TiO₂ nanotubes are shown in Figure 3(a). In terms of pure TiO₂ nanotubes, Ti, O, and C elements were detected at 459.6, 531.2, and 285.5 eV, respectively. Among these elements, carbon is supposed to be contaminant deposited at the surface of TiO₂ nanotubes. The surfaces of N-doped TiO₂ nanotubes were composed of Ti, O, N, and C contaminants, and a very weak N signal was detected at the surface of N-doped TiO₂ nanotubes. The XPS analysis also resulted that the N amounts in undoped TiO₂ nanotubes and N-doped TiO₂ nanotubes were 0.57 and 3.39 atomic%, respectively. The atomic ratio of Ti to N of N-doped TiO₂ nanotubes was 5.13. As previously reported, the photocatalytic effect of N dopant was affected by both the N content of N-doped TiO₂ and the degree of nitrogen atoms reacting with TiO₂ precursor [30]. Therefore, N-doped TiO₂ nanotubes having high N amounts and the atomic ratio of Ti to N are supposed to result in enhanced photocatalytic activity by visible light irradiation.
Figure 1: SEM images of 100 nm TiO$_2$ nanotubes with (a) 0.05 M, (b) 0.1 M, and (c) 0.2 M of DEA treatment. (d) TEM and (e) high-magnification TEM images of 100 nm TiO$_2$ nanotubes with 0.1 M DEA treatment.

Figure 2: X-ray diffraction patterns of undoped and nitrogen-doped TiO$_2$ nanotubes treated by 0.1 M DEA.

Also, the N amount doped in TiO$_2$ structure is related to the intensity of photocatalytic activity at visible light region, and N amount is affected by the reaction temperature of dopant and TiO$_2$. Previous studies have reported 5–8 atomic% of nitrogen incorporation into the TiO$_2$ surface by chemical treatment and excellent photocatalytic activity in the visible light region [30–32]. These studies involved heat treatment of N-doped TiO$_2$ nanoparticles at temperatures of 800–900 $^\circ$C to maximize the concentration of nitrogen doping. However, we could not heat treat TiO$_2$ nanotubes above 500 $^\circ$C because heat treatment above 500 $^\circ$C resulted in the formation of rutile structure destroying the nanotubular structure of TiO$_2$. This limitation provides lower N amount of TiO$_2$ nanotubes compared to that of other TiO$_2$ nanoparticles. There are several researches obtaining highly N-doped TiO$_2$ nanomaterials without conventional sintering process. Xiang et al. developed nitrogen-, sulfur- or carbon- doped TiO$_2$ nanosheets with exposed (001) facets showing excellent photocatalytic activity at visible region by solvothermal process [29, 33, 34]. Also, solvothermal process is seemed to be one of the techniques enhancing N-doping into the structure of TiO$_2$ nanotubes without the destruction of nanotubular structure as previously reported [24, 26]. Further experiment is required to investigate the comparison of the photocatalytic activity between sintering process and solvothermal process for doping nitrogen into TiO$_2$ nanotubes.

The N 1s peaks were detected at the surface of N-doped TiO$_2$ nanotubes at 406.1 and 402.5 eV of binding energy, respectively (see Figure 3(b)). In terms of the location of nitrogen dopant in TiO$_2$ structure, many researches have reported that nitrogen species are doped into TiO$_2$ in different forms due to doping process, reaction technique, and nitrogen sources [24–27, 29, 33–38]. From the results of previous researches [35–37], typical N 1s peak of TiN species mainly in substitutional N was less than 397.5 eV, whilst interstitial N in TiN species showed above 400 eV of typical N 1s binding energy. From the results of XPS analysis, typical binding energies of 402.5 and 406.1 eV are assigned to NO and NO$_2^-$ generating highest localized state for interstitial species, which are characteristics of interstitial N-doped TiO$_2$.
on the basis of previous studies [35–37, 39]. Thus, it is confirmed that nitrogen from DEA is effectively doped into TiO$_2$ nanotubes, and the N 1s peaks obtained from this study are assigned to interstitial N-doped TiO$_2$ nanotubes.

Figure 4(a) shows the cross-sectional views of water droplets on machined Ti, electropolished Ti, and undoped and N-doped TiO$_2$ nanotubes. Electropolishing did not change the hydrophilicity of Ti surface dramatically, but nitrogen doping did change the wettability of TiO$_2$ nanotubes by changing the hydrophilic surface to a super hydrophobic (>120°) surface. Therefore, we are investigating the effect of the super hydrophobicity of N-doped TiO$_2$ nanotubes on the behavior and functionality of human mesenchymal stem cells.

Presented in Figure 5 is the effect of PLA on the release behavior of antibacterial drugs such as tetracycline, CPC, and chlorhexidine. As shown in Figure 5(a), the experimental group with 10% tetracycline shows only an initial burst of drug release in the incubation period. However, all experimental groups with 1% PLA show sustained release of drugs as a function of incubation time. Therefore, we confirmed that 1% PLA could alter the elution behavior of all drugs and allow sustained and prolonged drug release regardless of the drug type.

Figure 6 shows the elution concentrations of the three antibacterial drugs loaded on the surface of undoped and N-doped TiO$_2$ nanotubes, respectively, after 30 seconds of visible light irradiation with the dental curing unit. In
Figure 5: The release amounts of antibacterial drugs as a function of incubation time. (a) 10% tetracycline mixed with/without 1% PLA. (b) 10% CPC and chlorhexidine mixed with 1% PLA.

Figure 6: (A) Dental light curing unit and visible light irradiation. (B) The concentration of drug released by visible light irradiation. (a) 10% Tetracycline, (b) 10% chlorhexidine, and (c) 10% CPC with 1% PLA.
the tetracycline and chlorhexidine elution tests, the release concentrations of drugs from N-doped TiO$_2$ nanotubes were significantly higher than those from undoped TiO$_2$ nanotubes ($P < 0.05$). However, the total amount of CPC released was much lower than the amounts of tetracycline and chlorhexidine, and there was no significant difference between CPC release from undoped and N-doped TiO$_2$ nanotubes.

On the basis of these results, we can summarize that nitrogen doping into the TiO$_2$ nanotubular structure was performed successfully by DEA treatment, even though the amount of nitrogen doping was lower than reported in other studies because of the lower heat treatment temperature used in this study. Moreover, drugs stored in N-doped TiO$_2$ nanotubes were released effectively by the visible light irradiation with the dental light curing unit.

4. Summary

The visible light irradiation-mediated drug elution activity of nitrogen-doped TiO$_2$ nanotubes has been investigated in this study. We found that nitrogen was effectively doped into the TiO$_2$ nanotubular structure, with the existence of NO$_2^-$ (406.1 eV) detected by the XPS analysis playing an important role in the photocatalytic activity of TiO$_2$ in the visible light region. The results of the drug release test showed that PLA facilitated sustained and prolonged elution of drugs. We conclude that N-doped TiO$_2$ nanotubes are expected to overcome the limited usage of TiO$_2$, which shows photocatalytic activity only within the UV region, thereby allowing the development of novel fusion technologies in the field of implant materials.

Conflict of Interests

The authors declare having no conflict of interests about all materials in this paper.

Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2011-0024067). The authors also thank the Wonkwang University of Regional Innovation Center For Next Generation Industrial Radiation Technology for the use of FE-SEM and XRD.

References


Submit your manuscripts at
http://www.hindawi.com