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Drug delivery behavior of titania nanotube arrays coated with chitosan polymer

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ABSTRACT

Titania nanotube (TNT) arrays with the length to diameter ratio of 85:1 were synthetized after anodizing the specimens at the anodizing voltage of 55 V for 2 h. Ultrasonic cleaning procedure in deionized water caused the formation of micro-cracks, clusters of TNT bundles and distortion of the nanotubes; however, acetone medium decreased the risk of fracture and the formation of clusters. To control the drug delivery rate, chitosan polymer was deposited on the surface of TNTs using dip-coating process. The total release of TNTs with 0, 0.29 and 0.45 μm chitosan coating thickness was about 6, 8 and 12 days, respectively.

1. Introduction

Inflammation and bacterial infection are the most serious complications after orthopedic surgeries [1–5]. Systemic drug administration cannot be considered as a proper solution to eliminate these problems as a result of some restrictions, such as low drug solubility, poor distribution [1–4], uncontrolled pharmacokinetics [1,2], poor targeting and serious side effects in non-target tissues [1–3,5–7]. Therefore, new drug delivery systems are required to release drugs at a specific rate and dosage in the target tissues [1,5,6].

Local drug delivery has several advantages over conventional drug delivery systems including lower required dosage, lower probability of promoting antibiotic resistance, extended release time, possibility of combining systemic and local drugs with different kinetics and controlled drug release directly to the required location [8].

Titania nanotube (TNT) arrays have been of interest for years as an excellent candidate for drug delivery systems due to their excellent biocompatibility [1,2,9,10], bioactivity [1,6,11–14], high surface area [2,5,13,15,16], thermal and chemical stability [2,3,7] and capability of loading and releasing drugs *in vivo* [1,2,5,17]. One of the best methods to use TNTs as a drug delivery system is in the form of a coating on the surface of metallic implants. Table 1 shows drug delivery from titanium nanotubes coated on a metallic substrate, their release mechanisms, test conditions, experimental model, outcome and applications [18–22]. TNTs have a porous structure which enables them to be loaded with therapeutic agents such as antibiotics [23], antimicrobial ionic agents [19] and microbial peptides [20] which makes them an excellent candidates for local drug delivery systems.

Anodization is a cost effective method [15,24–28] to produce TNT arrays with the ability to control the dimension of nanotubes [2,5,7,16,24]. In addition, drug delivery systems should be compatible with a range of therapies, disease condition and target tissue [7]. Drug release can be controlled by coating a polymeric layer on the surface of TNT arrays [1,5,7]. Chemical characteristics [2], biodegradability and the thickness of polymer [2,3,7] are the parameters that impact the drug release rate.

Chitosan has excellent bioactivity, good biodegradability and shows antibiotic and immunologic activities which make it an excellent candidate as a coating on TNTs [24]. Furthermore, it is

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Table 1
Drug delivery from titanium nanotubes coated on a metallic substrate, their release mechanisms, test conditions, experimental model, outcome and applications. Reprint with permission from [22].

Drug delivery system	Drug Model	Experimental model	Results	application
Antibiotic loaded titania nanotubes anodized from titanium	Gentamicin	*Staphylococcus epidermis*	Gentamicin-loaded nanotubes were effective in minimizing initial bacterial adhesion and these surfaces also supported higher cell adhesion and proliferation up to 7 days of culture compared to titanium surfaces.	Prevention of bacterial adhesion to implant surfaces.
Release of drug from composite PLGA/TiO2 nanotubes on Ti implant surface	Ibuprofen	PBS at pH 7.4 and 37 °C	Using a combination of PLGA and TiO_2 nanotubes increased drug release rates from 100% in 30 min, to 5 days (low molecular weight PLGA) and 9 days (high molecular weight PLGA).	Improvement in drug delivery release rates and promotion of bone growth.
Release of therapeutic agents from TiO_2 nanotube arrays on titanium surfaces	Vancomycin, silver	PBS at 37 °C	The increased surface area of the nanotubes increases the potential amount of drug that can be loaded onto the implant surface. The release kinetics can be tailored by adjusting the anodizing parameters and electrolyte composition.	Delivery system of antimicrobial agents.
TiO_2 nanotube arrays loaded with antimicrobial peptides (AMPs) on titanium implants	HHC-36 Broad spectrum AMP	*S. aureus*	HHC-36 was loaded into TiO_2 nanotubes via vacuum-assisted physical absorption. Anatase nanotubes showed better AMP loading than amorphous phase. AMP/TiO_2 surface significantly killed *S. aureus* and reduced bacterial adhesion.	Prevention and reduction of periimplant infections.

All the experiments were performed *in vitro*. Released mechanism was based on diffusion.

proved that the modification of chitosan polymers by dip-coating process can improve the osseointegration of dental and orthopedic implants [1–3,7].

The aim of the present study was to produce titania nanotube arrays by anodization method. The influences of anodization time, ultrasonic cleaning time and medium, and chitosan polymer coating thickness on the drug release rate of TNT arrays were studied. The results of this paper will open a new horizon to the next generation of drug delivery systems with a controlled drug release rate. Applying a chitosan polymer coating on the surface of TNTs could be a suitable technique in dental and orthopedic implants to avoid any infections after surgery with desired and sustained drug release.

2. Materials and methods

2.1. Fabrication of TNT arrays

Titanium foils (99.7% purity, Sigma–Aldrich Co) with a thickness of 0.25 mm were utilized as a substrate. Foils were cut into 1-cm square specimens and were cleaned by sonication for 15 min in acetone, ethanol and deionized water, successively. Electrochemical anodization was carried out in a two-electrode system with the Ti foil as the anode material and the platinum foil (1 cm × 1.5 cm) as the cathode material. Anodization was performed under magnetic stirring with an anodizing voltage of 55 V using a power supply (Mean Well, RS-50-48) for 1 and 2 h. The electrolyte consisted of 0.3 wt.% ammonium fluoride (NH_4F) (ACS reagent, ≥98.0% purity) and 2 wt.% deionized water in ethylene glycol (anhydrous, 99.8% purity, Sigma–Aldrich Co). The distance between the electrodes was 2 cm and all the experiments were conducted at room temperature. After anodization, the films were immersed in ethanol for 30 s to remove electrolyte traces and then were dried with nitrogen gas. The surface morphology of the specimens was studied using a field emission scanning electron microscope (SEM) (TESCAN, MIRA3-LM).

2.2. Surface debris removal from TNTs

In order to remove surface debris from TNTs, the samples were cleaned by an ultrasonic cleaner (Wise Clean WUCA O3H). Two series of samples were prepared. In the first one, the as-anodized Ti foils were ultrasonically cleaned with deionized water up to 15 min. In the second one, acetone was selected as a medium in the ultrasonic cleaning procedure. All the specimens were dried under a flow of N_2 gas. The effects of the solutions and the required time to clean the samples efficiently, were evaluated by SEM (TESCAN, MIRA3-LM). Furthermore, elemental analysis of the TNTs was evaluated by Energy-dispersive X-ray spectroscope (EDX) (SAMx, Idfix) to make sure no debris remains in or outside TNTs.

2.3. Heat treatment of TNTs

It is reported that nanotube arrays synthesized by anodization method have an amorphous crystallographic structure and subsequently annealing at high temperatures (around 580 °C) is required to have a crystalline structure [25]. Therefore, the ultrasonically cleaned TNTs were annealed at 580 °C in air for 3 h with the heating/cooling rate of 5 °C/min [2]. The phase transformation occurred after annealing was investigated by X-ray diffractometry (XRD) using a Stoe diffractometer with Cu Kα radiation (λ = 0.154056 nm). The XRD patterns were recorded in the 2θ range of 20–90° (step size of 0.04° and time per step of 1 s) at a voltage of 40 kV and a current of 30 mA.

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