Colloids and Surfaces B: Biointerfaces 143 (2016) 447–454

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Nanoporous anodic titanium dioxide layers as potential drug delivery systems: Drug release kinetics and mechanism

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ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form 22 March 2016
Accepted 24 March 2016
Available online 25 March 2016

Keywords:
Titanium dioxide
Drug delivery systems
Ibuprofen
Gentamicin
Anodization

ABSTRACT

Nanoporous anodic titanium dioxide (ATO) layers on Ti foil were prepared via a three step anodization process in an electrolyte based on an ethylene glycol solution with fluoride ions. Some of the ATO samples were heat-treated in order to achieve two different crystallographic structures – anatase (400 °C) and a mixture of anatase and rutile (600 °C). The structural and morphological characterizations of ATO layers were performed using a field emission scanning electron microscope (SEM). The hydrophilicity of ATO layers was determined with contact angle measurements using distilled water. Ibuprofen and gentamicin were loaded effectively inside the ATO nanopores. Afterwards, an in vitro drug release was conducted for 24 h under a static and dynamic flow conditions in a phosphate buffer solution at 37 °C. The drug concentrations were determined using UV–Vis spectrophotometry. The absorbance of ibuprofen was measured directly at 222 nm, whether gentamicin was determined as a complex with silver nanoparticles (Ag NPs) at 394 nm. Both compounds exhibited long term release profiles, despite the ATO structure. A new release model, based on the desorption of the drug from the ATO top surface followed by the desorption and diffusion of the drug from the nanopores, was derived. The proposed release model was fitted to the experimental drug release profiles, and kinetic parameters were calculated.

1. Introduction

Nowadays more and more people are suffering from an old age related diseases such as osteoarthritis. Statistics show that more than 90% of the population over the age of 40 have problems associated with the skeletal system and are at the risk of an orthopedic surgeries. However, implantable devices, implants, and grafts are capable of failure and their surgical placement into the body can result in post-operative complications including a lack of tissue integration, bacterial infections or osteomyelitis [1]. One of the most dangerous side effects associated with implants are bacterial infections, mainly caused by strains of *Staphylococcus aureus* that are able to form a surface biofilm which can weaken an interface between an implant and a surrounding tissue [2–5]. Another problem related to such infections is the resistance of bacteria to the conventional antimicrobial treatments [6,7]. Among limitations of conventional drug delivery systems (DDS) used in the systematic therapy, a finite solubility of drugs, leading to maldistribution and poor clinical efficacy, is one of the major problems [8–11]. Therefore, new implantable biomaterials with extended utility and increased functionality as a local DDS are extensively investigated.

With the development of nanoscience and nanotechnology, drug coated implants based on nanomaterials have become promising alternatives to address the problem. Not only the appropriate coatings that enhance cell adhesion and growth on orthopedic implants, but also functional materials used as DDSs with prolonged drug release profiles are desired [9,12–14]. Among nanoporous materials with pore sizes less than 100 nm, titanium dioxide layers are extensively investigated as potential materials for orthopedics and dental implants due to their good biocompatibility and desired mechanical properties [9,12,15–17]. Titanium and its alloys are nowadays one of the most commonly used materials for endosseous dental implants and endoprostheses because of their excellent biocompatibility, corrosion resistance and a relatively low elastic modulus. Bonding between the implant and bone occurs via an oxide layer created on the surface of Ti, when exposed to oxygen. The process is however long-lasting. There is a possibility to form the oxide layer on the Ti foil prior to the implanting. One of the methods used for the fabrication of nanoporous titanium dioxide layers is anodization. This procedure assures the good control

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http://dx.doi.org/10.1016/j.colsurfb.2016.03.073
0927-7765/

of pore diameters and the thickness of the oxide layer. In addition, the nanoporous anodic titanium dioxide (ATO) structure allows to load, store and release drug compounds. By changing anodization conditions, both the pore diameter and the length of porous layer may be changed, therefore, the rate and duration of the drug release can be altered [18–22]. The drug release characteristics is affected not only by geometrical parameters of ATO layers (pore diameter, porosity, layer thickness etc.) but also by the crystalline structure of TiO_2, namely anatase, rutile and brookite [21]. The as-prepared ATO layers are typically amorphous. However, by heat treatment, conversion of amorphous titania to anatase, mixture of anatase and rutile, and pure rutile phases can be achieved [23]. The temperature related transformation of oxide plays an important role in an improvement of the cell growth. The published studies indicate that anatase facilitates a bone cell attachment, proliferation and differentiation [24]. Nonetheless, there is no significant difference in the amount of the released drug between annealed and unannealed ATO layers [25].

Gentamicin (GM), a representative of aminoglycoside antibiotics, was isolated from the actinomycete *Micromonospora purpurea* in 1963. Due to its effective activity against gram-negative bacteria, such as *Pseudomonas*, *Proteus*, and *Serratia*, this antibiotic has been widely used in implantology since 1971 [26,27]. Gentamicin is composed of a number of related gentamicin components such as C1, C1a, C2, C2a and C2b [28]. In order to treat bacterial infections that can occur after orthopedic operations, gentamicin has to be administered intravenously, intramuscularly or topically [27]. One of the side effects of taking gentamicin is its selective accumulation in renal proximal convoluted tubules that results in loss of its brush border integrity [27]. Since gentamicin-induced nephrotoxicity occurs at high local levels of the drug with low systemic toxicity, the best solution is to deliver gentamicin directly at the interface between implant and tissue [29]. Nonsteroidal anti-inflammatory drugs, such as ibuprofen (2-[3-(2-methylpropyl)phenyl]propanoic acid), are commonly used to treat fever, pain or arthritis [30,31]. Despite the good therapeutic effect of ibuprofen (IBU), its high doses can cause gastric irritation. Therefore, it should be delivered via the parenteral route only to the site of the infection, preferentially using local drug delivery systems [32].

The aim of the ideal drug delivery system is to maintain the drug concentration at the desired therapeutic level for a long period of time. Therefore, it is important to control the rate and duration of the drug release. To predict and control the amount of the released active substance from the DDS, the mathematical formulation that describes the kinetics of drug delivery process is necessary to be deduced. In the literature, there are plenty of theoretical or empirical models such as the Korsmeyer–Peppas, first order kinetics, Higuchi and Gallagher–Corrigan [33,34] models describing drug release processes. Most of them indicate that the initial and rapid release of the drug is followed by a slow delivery of the component [35,36]. The aim of this study was to examine the drug release profiles from anodic titanium dioxide layers. Gentamicin and ibuprofen, as representatives of antibiotic and anti-inflammatory drugs, respectively, were used as model compounds for release tests. Both static and dynamic release conditions were tested. Drug release profiles were examined in detail, and a new mathematical model was proposed. In addition, a mechanism of drug release from nanoporous ATO layers, being a combination of desorption and diffusion processes, was provided.

2. Experimental

2.1. Preparation of nanoporous anodic titanium dioxide layers on Ti foil

The titanium foil (99.5% purity, 0.25 mm thick, Alfa Aesar) was pre-cut in coupons (1 cm × 2 cm) and degreased in acetone and ethanol. Afterwards, the samples underwent electrochemical and chemical polishing [37], and were rinsed with distilled water and ethanol. Finally, the polished samples were air-dried. Then, the samples were painted with an acid resistant paint leaving a working area of 1 cm × 1 cm. A three-step anodization process was used to obtain the ATO layers. As the anodizing electrolyte, an ethylene glycol solution containing NH_4F (0.38 wt.%) and H_2O (1.79 wt.%) was used. The anodization conditions were as follows: potential—40 V and temperature—20 °C. The process was carried out in a two-electrode cell, where the Ti sample was used as an anode and the Ti plate as a cathode. The first and second anodizing steps were carried out for 3 h, whereas the third step lasted 10 min. It is worth mentioning that after first two steps the created oxide films were removed by mechanical detachment using an adhesive tape. Before the third anodization, the electrochemical cell was filled with the fresh electrolyte. The pore diameter of the received structures was around 65 nm. The thickness of the grown ATO layers was approximately 2.1 μm which was assessed using SEM cross-section images of obtained layers.

2.2. Modification of the crystalline structure

The as-anodized samples of titania possess an amorphous structure. In order to change their crystallographic structure, ATO layers were annealed in air at two different temperatures (400 and 600 °C) for 2 h using a muffle furnace (model FCF5-SHM Z, Czylok). The heating rate was 2 °C min^{-1}. As a result, the anatase and a mixture of anatase and rutile phases were obtained, respectively. The structural and morphological characterizations of both amorphous and annealed samples were performed using a field emission scanning electron microscope (FE-SEM, Hitachi S-4700).

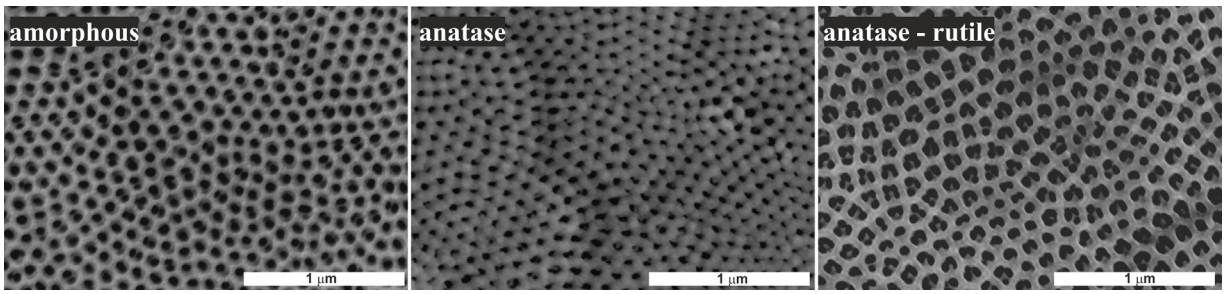

Fig. 1. SEM images of nanoporous TiO_2 layers formed in the ethylene glycol-based electrolyte at the constant anodizing potential of 40 V at 20 °C. Amorphous – as prepared, annealed at 400 °C – anatase, and annealed at 600 °C – mixture of anatase and rutile are shown, respectively.