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Release behaviors of drug loaded chitosan/calcium phosphate coatings on titanium

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ABSTRACT

Implants with antibiotic drug loaded bioactive coatings have been increasingly applied in orthopedic operations. Here we report the drug release behavior of gentamycin loaded chitosan/calcium phosphate coatings on titanium. Chitosan/calcium phosphate coatings with different component ratios and surface topographies were prepared by electrochemical deposition method. Our results showed that the drug release from these coatings was controlled by their component ratio and surface topography, and the former ratio played a more significant role. The present coatings could provide an effective way to create both good bioactivity and antibacterial activity.

1. Introduction

Coatings that exhibit with both bioactivity and anti-inflammation properties are required in clinic surgery. Titanium implants with bioactive calcium phosphate (Ca–P) coatings have been used in hard-tissue replacement in orthopedics [1]. However, pure Ca–P coatings are normally inefficient in drug loading and releasing due to the lack of appropriate accommodating microstructure and chemical bonding [2]. Different efforts have been directed at improving the drug loading ability of these coatings [3,4]. The incorporation of biopolymers to the coating has been proven to be an efficient way of improving their drug loading capabilities [5].

Chitosan, a natural cationic polysaccharide, has been used in a number of biomedical applications, including as a drug carriers [6]. Chitosan has been incorporated into the Ca–P coating to improve its drug loading ability [5,7]. Chitosan/Ca–P scaffold could act as an ideal drug delivery carrier of antibiotic drug [5,8]. Hence, the chitosan/Ca–P coating is ideal for both bioactivity and drug release.

Among all available methods for chitosan/Ca–P coating, the electrochemical deposition method demonstrates a variety of advantages, such as low process temperature, low cost, a high degree of thickness-control and straightforward deposition on irregular substrates [8–10]. Besides Collagen/Ca–P coatings, a chitosan/octacalcium phosphate coating was also prepared by the electrochemical deposition process [11,12].

As one of the amino-glycosides, a diverse class of antibiotics gentamycin is widely used in orthopedic applications [13]. Gentamycin is effective against Gram-positive and Gram-negative aerobic organisms [14,15], and can be quickly adsorbed and excreted. Therefore, gentamycin is commonly used to evaluate the drug loading and releasing ability of materials [4,16].

In this study, chitosan/Ca–P coatings with different component ratio and surface topographies were prepared by an electrochemical deposition process. The drug loading and releasing capacity and releasing rate of the coatings were evaluated. The relationship between release behaviors and the component ratio and surface topography is briefly discussed.

2. Materials and methods

2.1. Coating preparation

A piece of titanium plate (10 mm × 10 mm) was treated in diluted acid (mixture of nitric acid and hydrofluoric acid), then rinsed with de-ionized water, and mounted as the working electrode. A platinum plate was used as the counter electrode. The distance between the two electrodes was fixed at 15 mm. The electrolyte solution was prepared by adding 30–10 mM $Ca(NO_3)_2$ (Shanghai Chem. Co., China) and 10–0 mM NaH_2PO_4 (Shanghai Chem. Co., China) into 0.5 g/100 mL chitosan (Shandong Aokang Chem. Co., China). The pH was adjusted to 5.8. The working voltage was set at 2.8 V and the deposition time was 30 min. The as-deposited coatings were washed with de-ionized water and dried. The experimental conditions of each coating are listed in Table 1.

2.2. Coating characterizations

The morphology and microstructure of the samples were characterized by scanning electron microscopy (SEM, Hitachi, S4800) and transmission electron microscopy (HRTEM, TECNAI, G2 F30 S-TWIN). Composition and phase determination was done via X-ray diffraction (XRD, X' Pert PRO, CuKα, 2°/min, 0.02 per step). Fourier transform-infrared spectroscopy (FTIR, Thermofisher iS10) was employed to reveal the chemical bonding of the deposited coatings.

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Table 1
List of the samples with different calcium and phosphate concentration in the electrolyte solutions.

Sample	$Ca(NO_3)_2$ mmol/L	NaH_2PO_4 mmol/L
Porous chitosan/Ca–P (PCP) coating	30	10
Micro porous chitosan/Ca–P (MCP) coating	10	10
Dense chitosan (DC) coating	30	0

2.3. Drug loading and releasing evaluations

The drug loading properties were determined by dynamic contact-angle obtained through a contact-angle meter (Dataphysics, OCA20). The release of gentamycin with quantitative drug loading was examined by ultraviolet-visible spectrometry (TU1901) with an indicator of Evans blue (CAS: 314-13-6 Shyysw Co).

The dynamic contact-angle measurement could be used to analyze the interface behavior of a drop of the drug on the coating surface [17]. A camera was equipped to record the volume change of the droplet of the drug on the coating surface. In this study, 5 μL of GS solution was dropped onto chitosan/Ca–P coating surface. During de-wetting, the average rate of the drop volume loss, which could represent the velocity of drug drop infiltrated into the sample coatings, could be calculated. The drop volume left after de-wetting could represent the capacity of drug loading.

The absorption peak intensity of Evans blue decreased substantially after the several milligrams of Gentamycin was added in to the assay. The reagent of Evans blue 1×10^{-4} mM has been proven to be sufficient enough to detect antibiotic presence in the assays [18]. Standard solutions (1 to 10 mg/L) were prepared from a stock solution of 40 mg/L gentamycin in the physiological saline, which generated reliable standard curves.

Gentamycin sulfate (GS) solution (40 mg/mL) was prepared by dissolving gentamycin sulfate powder ($C_{21}H_{43}N_5O_7.H_2SO_4$ CSA: 1405-41-0 Shyysw Co.) into de-ionized water. The drug droplet was added to the chitosan/Ca–P coating's surface carefully by a transferpette. The addition of drug volume was controlled at 25 μL. The drug loading surface was fixed at $0.5cm^2$ (5 mm × 10 mm). After loading, the coatings were dried at 37 °C for 24 h.

The loaded coatings were immersed in 5 mL physiological saline, whose concentration was 0.9% NaCl, and were kept at 36.7 °C, to simulate body fluid in vivo. The physiological saline solution was refreshed at 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min, 75 min, 90 min, 180 min, 1 day, 2 day, and 3 day, to analyze both short term and long term behavior. The concentration of gentamycin in the physiological saline was determined by ultraviolet-visible spectrometry (TU1901). Each group contained three parallel samples.

The coatings were soaked into the GS solution (40 mg/mL) for 10 min, then were taken out and dried for 24 h. The loaded coatings were immersed in 10 mL of physiological saline solution for 30 min for the evaluation of the release of gentamycin. Each group also contained three parallel samples.

3. Results and discussion

3.1. Coating characterizations

The resultant coatings developed into a porous structure with the increase of calcium and phosphate concentration in the electrolyte solutions. As showed in Fig.1, the dense chitosan (DC) coating derived

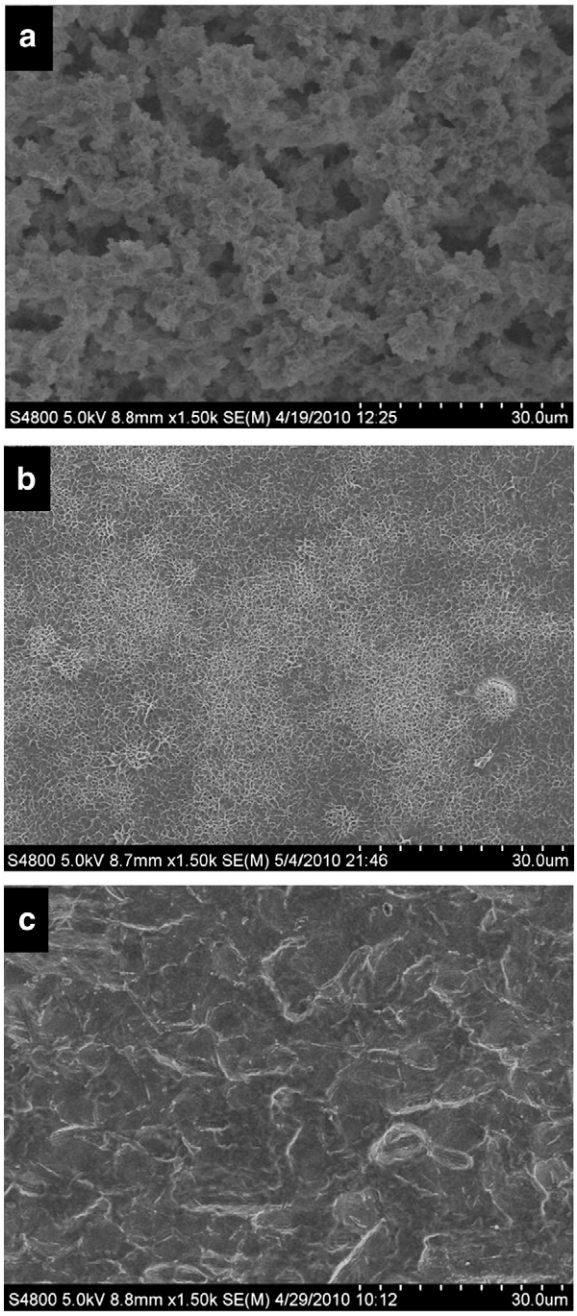

Fig. 1. SEM images of (a) PCP coating; (b) MCP coating; (c) DC coating.

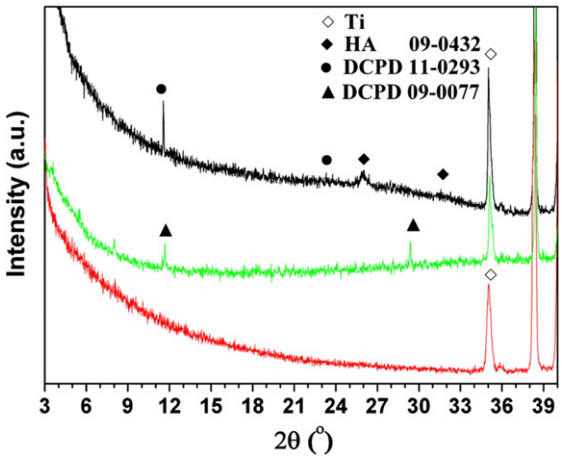

Fig. 2. XRD spectra of (a) PCP coating; (b) MCP coating; (c) DC coating.