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Design and characterization of a novel biocorrodible iron-based drug-eluting coronary scaffold

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ABSTRACT

Long corrosion period and slow resorption in vivo remain major limitations for iron-based bioresorbable scaffolds. This work focused on the design and characterization of a novel iron-based drug-eluting coronary scaffold (IBS scaffold) made of nitrided iron materials. The 53 μm IBS scaffold shows good device performance comparable to a current mainstream drug-eluting coronary stent (Xience Prime™) due to the good comprehensive mechanical performance of nitrided iron materials. The novel design of a zinc barrier layer makes it possible for the IBS scaffold to have ultrathin struts and thick PDLLA coating of 12 μm to maintain adequate scaffolding (125 kPa) after 3 months implantation while having a significantly shortened corrosion period (13 months). The biocorrosion and bioresorption of the IBS scaffold could be effectively evaluated using Micro-CT, OCT and MRI methods. Although complete bioresorption of the corrosion products has not been observed yet, there are no identified biological problems for the IBS scaffold after implantation in rabbit abdominal aorta up to 13 months. This study demonstrates that the IBS scaffold with novel design has significantly shortened corrosion period and less amount of corrosion products without causing any biological problems after implantation up to 13 months, therefore is promising for coronary application.

1. Introduction

Bioresorbable scaffolds have been acknowledged to be the 4th revolution in vascular intervention after the 1st revolution of plain old balloon angioplasty (POBA), the 2nd revolution of bare metal stents (BMSs) and the 3rd revolution of drug-eluting stents (DESs) [1]. An ideal bioresorbable scaffold should have good mechanical performance, good biocompatibility and reasonable degradation and absorption period [2]. So far, the bioresorbable scaffold family currently being researched and developed mainly includes the polymer-based, Mg-based, Zn-based and Fe-based scaffolds [3,4,5].

Polymer-based scaffold presents the highlighted research direction due to technology accumulation in polymers especially the polylactic acid (PLA) material in the last decades. There are numerous devices available for preclinical and clinical evaluation, among which three have been CE marked for sale [6]. However, the inherent defect for this scaffold is its poor mechanical performance, which limits its use in complex lesions with narrowed indications [6]. Mg-based scaffolds have been widely investigated and now in the stage of clinical trial due to better mechanical performance than polymeric scaffolds and good biocompatibility, however, they corrode too fast to maintain effective scaffolding in the first 3–6 months and have their own problem of hydrogen evolution [4]. Zn and its alloys have also been developed for bioresorbable vascular scaffold nowadays [7,8]. Although good biocompatibility and probably suitable corrosion rate have been reported for Zn and its alloys in some studies [9,10], their mechanical performance needs further improvement [11,12].

As candidate material for bioresorbable scaffolds, iron and its alloys have been demonstrated to have good mechanical performance [13,14] and biocompatibility [15,16,17]. However, long corrosion period and slow clearance of their solid corrosion products remain major limitations for iron-based bioresorbable scaffolds [4,18,19]. The corrosion period of iron-based scaffold can be shortened by accelerating the material corrosion and/or by decreasing the scaffold mass/volume. Recently, a lot of researches have been focused on increasing the corrosion rate of iron-based materials by alloy composition design [20,21,22,23], material structure design [24,25,26,27], material modification [28] and introducing corrosion-promoting substances or mechanisms [29,30]. However, rapid and localized corrosion of the iron-based scaffold would lead to new problems that the scaffold could not provide enough supporting to the lesion vessel wall in the early time after implantation

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and the rapidly formed and accumulated corrosion products might exceed tissue tolerance to bring biological risks. Moreover, both high strength and plasticity are essential for the iron-based materials in order to design a scaffold maintaining good device performance with decreased mass/volume [31,32]. However, so far, few studies have reported effective methods for the iron-based scaffold to achieve both superior comprehensive mechanical performance and short corrosion period without sacrificing biocompatibility. Undoubtedly, from material to device, there are still a lot of considerations [33–35].

In this study, an ultra-thin iron-based drug-eluting scaffold (IBS scaffold) with short corrosion period was designed and evaluated, compared with a current mainstream drug-eluting stent (DES). The coating design of the drug-eluting iron-based scaffold was characterized. Mass loss test, micro-computed tomography (Micro-CT), scanning electron microscope (SEM), energy dispersive spectrometer (EDS), optical coherence tomography (OCT) and magnetic resonance imaging (MRI) were used to follow up the corrosion evolution of the IBS scaffold. Histopathological observation was also carried out to further investigate the long-term local tissue response to the implanted IBS scaffold.

2. Materials and methods

2.1. Materials and animals

The 53 μm iron-based drug-eluting coronary scaffolds (IBS scaffold, Φ3.0 × 8 mm and Φ3.0 × 18 mm, strut thickness –53 μm) were manufactured by Lifetech Scientific Co., Ltd. (Shenzhen, China). Vacuum plasma nitriding as described in our previous work [36] was applied to the laser-cut pure iron scaffolds to obtain the nitrided iron scaffolds, after which polishing was carried out. The composition and microstructure of the nitrided iron scaffolds were reported in our previous study [36]. The polished nitrided iron scaffolds were weighed and further underwent zinc electroplating (~600 nm) and sirolimus-carrying Poly(D, L-lactide) (PDLLA, amorphous; Evonik Industries, Germany) coating (~12 μm) in sequence. All scaffolds were crimped onto the matching rapid-exchange balloon catheters (Φ3.0 × 8 mm and Φ3.0 × 18 mm, Lifetech Scientific, Shenzhen, China) to obtain scaffold systems, which were then sterilized. A current mainstream Co–Cr alloy stent system (Xience Prime™, Φ3.0 × 18 mm, Abbott Vascular, Santa Clara, CA, USA), 70 μm nitrided iron scaffold (Φ3.0 × 18 mm), 70 μm nitrided iron scaffold with 5 μm PDLLA coating (Φ3.0 × 8 mm) and 53 μm nitrided iron scaffold with 12 μm PDLLA coating (Φ3.0 × 8 mm) were chosen as controls.

In the implantation experiment, 24 IBS scaffolds (Φ3.0 × 8 mm), 18 nitrided iron scaffolds of 70 μm with 5 μm PDLLA coating (Φ3.0 × 8 mm) and 18 nitrided iron scaffold of 53 μm with 12 μm PDLLA coating (Φ3.0 × 8 mm) were deployed in the abdominal aorta of 20 adult New Zealand white rabbits, with 3 scaffolds of the same kind implanted in each rabbit. The right femoral artery was surgically exposed and a 5F guide catheter introduced over a 0.014 in. guidewire. Then the scaffolds were introduced and positioned in the abdominal aorta under fluoroscopic control. Balloons were inflated with 8 atm (nominal pressure) to 10 atm for 30s to deploy the scaffolds. Placing the scaffolds/stents across the orifice of major branches of the descending aorta was avoided. Selectively, 4 male rabbits and 4 female rabbits (mean weight 2.0 kg, range 1.6–2.4 kg) purchased from Pearl Laboratory Animal Science & Technology Co., Ltd. were fed with a standard diet without cholesterol or lipid supplementation throughout the experiment. The use of all experimental animals in the study was in accordance with accepted institutional policies and under the approval of the Ethics Committee of the Shenzhen Testing Centre of Medical Devices.

2.2. Device parameters and performance

2.2.1. Informative data

Scaffold metallic surface percentage @ nominal pressure, scaffold platform and coating material/thickness/mass, drug and its content are all informative data obtained from the product description of Lifetech Scientific and Abbott Corporation to help understand the device design, which were based on at least 20 valid data records for each testing item in each group.

2.2.2. Crossing profile

The crossing profile is defined as the maximum diameter found between the proximal end of the balloon and the distal tip of the catheter, which was tested under a digital microscope (VHX-700F, KEYENCE, Japan).

2.2.3. Radial strength

Curves of radial strength vs. scaffold outer diameter were measured at a compression rate of 0.1 mm/s using a radial strength tester (RX550-100, Machine Solution Inc., USA). Radial strength (kPa) is defined as the strength at 10% compression of the original scaffold outer diameter.

2.2.4. Maximal expansion diameter

The scaffolds with radial strength tested were then over-expanded using balloons with gradually-increasing inflation outer diameter, and record the maximal balloon inflation outer diameter under which the scaffold did not fracture. The maximal expansion diameter of the scaffold is defined as the minimum of the maximal balloon inflation outer diameter for each group.

Five samples (Φ3.0 × 18 mm) were tested respectively, for 70 μm nitrided iron scaffold group, IBS scaffold group, and Xience Prime™ group, with crossing profile, radial strength and maximal expansion diameter tested in sequence for each sample.

2.3. Crossing-section structure and composition

The IBS scaffold after Pt spraying was embedded in resin (EpoxiCure, Buler, USA) for 8 h curing. Then the strut crossing-section of the IBS sample was ground and polished for structure observation and composition analysis using scanning electron microscope (SEM, JSM-6510, JEOL, Japan) equipped with an energy-dispersive X-ray spectrometer (EDS, Oxford Inca Energy 350, Oxford Instruments, United Kingdom).

2.4. Implantation experiment

2.4.1. In vivo corrosion

Gross dissection observation has been conducted after euthanasia of the rabbits. Four of the six IBS scaffolded vessels explanted from two rabbits after 3, 6 and 13 months implantation, respectively, were immersed in NaOH solution (1 mol/L) for 12 h to dissolve tissue and ultrasonically cleaned in tartaric acid (3–5 wt.%), NaOH solution (1 mol/L), deionized water, and absolute ethyl alcohol in sequence to remove the corrosion products, and then weighed for calculation of relative mass loss using an electronic balance with an accuracy of 0.001 mg (ME5, Sartorius, Germany). Nitrided iron scaffolds of 70 μm with 5 μm PDLLA coating (Φ3.0 × 8 mm) and nitrided iron scaffold of 53 μm with 12 μm PDLLA coating were used as controls.

The remained two IBS scaffolded vessels explanted from two rabbits underwent Micro-Computed Tomography (Micro-CT, Skyscan1172, Bruker, Germany) 3D reconstruction, after 3, 6 and 13 months implantation, respectively. Three IBS scaffolds in one rabbit were explanted with vessel tissue for Micro-CT 3D reconstruction after 3 days implantation. Three IBS scaffolds in one rabbit were checked for corrosion extent using magnetic resonance imaging (MRI, MAGNETOM Avanto 1.5T, Siemens, Germany) and optical coherence tomography (OCT, C7 XR, LightLab Imaging, St. Jude Medical, Westford, Massachusetts) in sequence, after 3 days, 3 months, 6 months and 13 months implantation.