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In vivo evaluation and characterization of a bio-absorbable drug-coated stent fabricated using a 3D-printing system

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ABSTRACT

In this study, we prepared a helical, biocompatible, and biodegradable stent by 3D rapid prototyping. The fabricated polycaprolactone (PCL) stent was coated with sirolimus mixed with poly-(lactide-*co*-glycolide) (PLGA), and polyethylene glycol (PEG), via a spraying method for slow drug release. The engineered, drug-eluting, bio-absorbable vascular stent (BVS) was analyzed and tested *in vivo*, and proving effective in animal experiments. These findings suggest that our new approach is useful for treating coronary thrombosis, and it may provide a promising scaffold for developing biological stent technology.

1. Introduction

Coronary disease has long been treated by percutaneous coronary intervention using stents. The established biological stents include bare metal stents (BMS), drug-eluting stents (DES), and bio-absorbable vascular stents (BVS) [1–5]. DES inhibit neointimal hyperplasia more successfully than BMS, using an antiproliferative drug in the bio-absorbable polymer coating [6]. However, stents directly loaded with a drug may cause an initial release of the drug that can lead to stent thrombosis, resulting in myocardial infarction or cardiac death [7,8].

As a novel stent, BVS might confer advantages, such as a reduction in restenosis, and the ability to degrade fully over time. In order to impart these benefits, BVS should be a strong biomechanical vascular support, sustain the release of a drug during the vascular healing process to prevent the proliferation of smooth muscle cells, and absorb materials after vascular healing.

Recently, three-dimensional (3D) printing, a specific technique in the biomedical field, has emerged as an alternative system for producing biomaterials. The 3D printing system, applied to rapid prototyping in structural fabrication can easily manufacture bio-materials, such as BVS, better than other devices. Additionally, 3D-printing offers a more efficient process for assembling all of the necessary components, such as the vascular artificial scaffold.

For the past decade, biomedical stents have received much attention for their prevention of coronary thrombosis. Conventionally used BMS, such as stainless steel and titanium, can cause after effects, as they remain *in situ* even after vascular repair. Thus, there is a need for residue-free alternatives. For these reasons, we fabricated a drug-eluting BVS polycaprolatone (PCL) stent using a 3D printing system, and we spray-coated it with the immunosuppressive drug sirolimus, to create a novel type of coronary stent. This current research is the first to design a drug-coated BVS in the area of vascular tissue engineering. The manufactured drug-coated BVS was characterized, and a porcine animal study was performed.

2. Material and methods

Commercially available PCL (M_w 4o kDa) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Poly-(lactide-*co*-glycolide) (PLGA) and polyethylene glycol, PLGA-PEG (M_w 103 kDa) were purchased from EVONIK (UK) and sirolimus was purchased from LC Laboratories

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(USA). All other chemicals and solvents were analytical or reagent and were used without further purifications.

The BVS PCL scaffold ($n=50$) was fabricated using a 3D printing system (Fig. 1a) and the specific method is presented in our previous report [9]. The strut size and between strand distances were 300 and 1300 μm, respectively.

An ultrasonic spray method was used to apply coatings to the BVS (Fig. 1b). The required amount of polymer PLGA-PEG 15 (PLGA with 15 wt% PEG [M_w 5 kDa]) and sirolimus were dissolved in 5 ml of tetrahydrofuran (THF). The drug solution was then dissolved in the polymer solution. The sprayed liquid consisted of the polymer/drug system dissolved in THF and diluted to 2% by weight. The operating requirements in this application called for flow rates of 50 μl/min. The stents were placed on a mandrel attached to a rotating shaft. The coated stents ($n=25$) were vacuum-dried for 24 h.

Surface morphologies were examined by scanning electron microscopy (SEM, SNE-1500M, SEC Co., Ltd). The samples were sputter coated with gold for 1.5 min and scanned at an accelerating voltage of 5 kV. The working distance used was approximately 18 mm during SEM. Drug-coated BVS is processed in the course of drug coating, drying, sterilization, and packaging for 4 days. To check weight loss in processing, drug-coated BVS was measured weight change by balance precision (HR-202i, AND, USA).

The drug-coated BVS were immersed in a tube containing 5 ml phosphate buffer solution (PBS; pH 7.4) for the degradation test and *in vitro* release test. This tube was held at 37 °C while being constantly agitated at 100 rpm in an incubator shaker (JEIO tech, Korea). At predetermined time points, this solution was collected and replaced with a fresh PBS. The release of sirolimus from the drug-coated BVS was measured using Nanospace SI-2 high pressure liquid chromatography (HPLC, Shiseido, Japan).

The animal study was approved by the Ethics Committee of Chonnam National University Medical School and Chonnam National University Hospital, and it conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Study animals were castrated male pigs ($n=3$) weighing 20–25 kg. More information about the animal experiments and histopathological analysis are presented in Fig. 4a and b, respectively.

3. Results and discussion

Fig. 1a shows a schematic of the 3D printing system. The fabricated BVS then underwent sirolimus coating via an ultrasonic spray method in order to prepare a DES (Fig. 1b). As shown in the

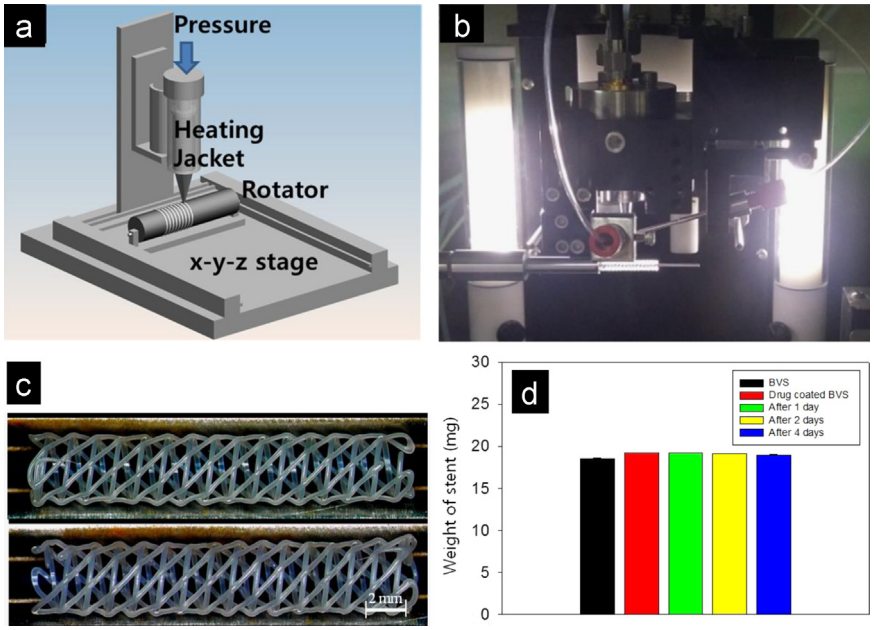

Fig. 1. Schematic design of a 3D printing system (a), an ultrasonic-spray coating system (b), an optical microscope image (c), and a weight changes (d).

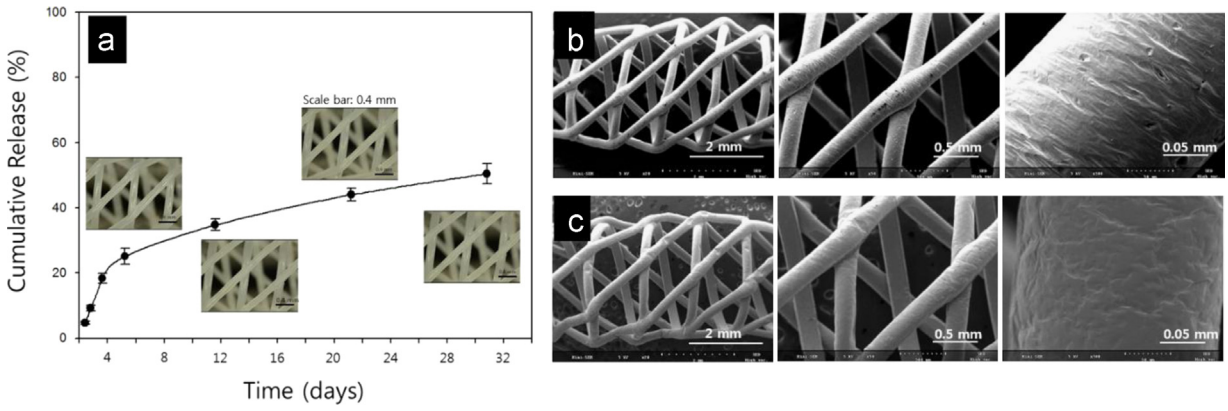

Fig. 2. Cumulative release of sirolimus (a) and SEM image of BVS (b) and sirolimus coated BVS (c) after zero day.