Core-shell Nanofibers-coated Drug-eluting Stents for Suppression of Restenosis

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ABSTRACT SUMMARY
Electrospun nanofibrous meshes have been employed as unique matrix for tissue engineering and drug delivery system due to their morphological characteristics such as high surface area and porous structures.\(^1\) Recently, our group reported that the coaxial nanofiber can be potentially tailored as a drug reservoir because the core and the shell of the nanofiber could be optimized for differential incorporation and release of proteins.\(^2\) Inspired by the coaxial nanofibers, we fabricated nanofiber-coated drug eluting stents where the core of the nanofibers contained paclitaxel (PTX) for suppression of restenosis. Drug-eluting nanofibers coated stents are expected to control the release of PTX as well as the high incorporation of the drug by coaxial electrospinning.

INTRODUCTION
Drug-eluting stents are employed for suppression of restenosis. However, the drug-eluting stent was hard to control release of drug. In this study, electrospun nanofibrous mesh were fabricated to core-shell structure using dual nozzle for high drug loading efficiency and control the release of drug. Coaxial electrospun nanofibrous were composed of polycaprolactone (PCL) and polyurethane (PU) so that the coated shells showed both good biodegradability and elasticity. PTX was encapsulated at the core for suppression of restenosis. For characterization of this nanofiber, Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) were performed for confirm the surface morphology and core-shell structure. Also, the coaxial nanofiber was measured for initial weight and was then placed in a test tube phosphate buffered saline (PBS) for in vitro degradation study. These drug-eluting nanofibers coated stents are expected to control the release of PTX for suppression of restenosis as well as the high drug loading efficiency by coaxial electrospinning.

EXPERIMENTAL METHODS
For the preparation of PU/ PCL nanofiber included PTX, a mixture of PU (SP80A) and PCL (3:7, w/w) was dissolved in chloroform for the outer solution. For the inner solution, PTX was dissolved in a mixture of Cremophor EL and ethanol to 5wt%. The outer solutions and the inner solution were simultaneously injected to the grounded stainless steel stents through the dual nozzle (18G/25G) at a flow rate of 1.0ml and 0.1ml/h, respectively and 15kV of the electric potential was applied between the needle and the ground. The coaxial structure of the nanofiber was examined by SEM and TEM. The loading amount of PTX in the core of the nanofibers was determined by reversed-phase HPLC at 227nm. The degradation profiles of the nanofibers were determined in PBS at 37°C for 3 months. All nanofibrous meshes were manually extended to simulate the expansion degree of the stents during the balloon catheter operation.

Figure 1. Schematic illustration of coaxial electrospinning using dual nozzles to fabricate PTX nanofiber-coated stents (optical microscopic image).
RESULTS AND DISCUSSION

PU/PCL coaxial nanofibers were electrospun on a stent according to the method shown in Figure 1. Thus, the electrospun fibers are composed of the core-encapsulated PTX surrounded by a PU/PCL mixture. The release of the PTX is controllable by PU/PCL ratios because PTX is expected to be diffused out through the polymeric walls. In Figure 2, the coaxial structure was confirmed by SEM and TEM, suggesting that the core of the nanofibers were covered with the thin-walled shells.

Figure 2. SEM image of PU/PCL electrospun nanofiber (a) and TEM image of coaxial nanofiber composed core-shell structures (b).

Figure 3 shows the mass erosion profiles of PU/PCL nanofibers in PBS at 37°C. The PU/PCL nanofibers degraded by 30.0±4.1% (w/w) for 91 day. Thus, the mass erosion of the nanofibers was confirmed to be dependent on the hydrolytic degradation of PCL.3

Figure 3. The degradation test profile of PU/PCL nanofiber incubated in PBS at 37°C and the SEM images shows the surface morphology change during the degradation.

In order to evaluate the PTX loading efficiency in the nanofibers, we electrospun the PTX-loaded nanofibers either by dual-nozzles or single nozzle. When the dual nozzle was employed, the loading efficiency was 89.6±19.8% while the value dropped to 1.4±1.2% in case of single nozzle process where the mixture of PTX and polymers were injected through one nozzle. We expected the core-encapsulated PTX was well-protected with the polymeric wall and PTX is not easily lost during the washing process. Figure 4 shows that the stent surface was well coated and contoured with thin layers of the PU/PCL coaxial nanofibers and morphology after expansion. The coated stent with nanofiber was allowed to be smoothly expanded by 3.3 times without any tearing. The diameter of PU/PCL coaxial nanofibers became thinner by 0.42 folds in comparison to those before expansion of the stent.

Figure 4. SEM images of stent covered with PU/PCL coaxial nanofiber. (a) SEM images of a covered stent before expansion and (b) after expansion. The nanofiber morphology images on stent surface were inserted, respectively.

CONCLUSION

The PU/PCL coaxial nanofibers were fabricated to core-shell structure using dual nozzle. The PU/PCL coaxial nanofibers were degraded upon exposure to PBS and have high drug loading efficiency. The nanofibers on stent surfaces were fabricated to sufficiently thin, flat and elastic to be smoothly extended with the expansion of metal stents.

REFERENCES