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Polymeric Nanofiber Coated Esophageal Stent for Sustained Delivery of an Anticancer Drug

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Abstract: In this study, we developed an esophageal stent capable of sustained delivery of an anticancer drug, fluorouracil (5-FU). The stents were coated with drug-loaded poly(lactic-*co*-glycolic acid) (PLGA) nanofibers (DPN) *via* the electrospinning method, which exhibited a sustained drug release for up to 6 days. To prolong drug release, we also added the nanofiber layers composed of PLGA alone (PN), surrounding the DPN layer, as a more resistive diffusion barrier, where a period of drug release could be extended to 21 days with the DPN layer topped with another 192 μm thick PN layer. Therefore, we envisioned longer period of drug release with the thicker PN layers, obtained simply with a longer collection time of PLGA nanofibers *via* electrospinning. Overall, we concluded that the drug-delivery esophageal stent prepared in this study is promising in the long-term treatment of dysphagia caused by esophageal cancer.

Keywords: drug delivery systems, electrospinning, esophageal stents, fluorouracil, poly(lactic-*co*-glycolic acid).

Introduction

Esophageal cancer ranks as the sixth most common malignancy in the world with a 5-year survival rate of less than 10%,[1] and is responsible for 15,000 cancer deaths in the United States and for 300,000 deaths in the world in 2009.[2] Although surgical removal of esophageal tumor could be a way of treatment, which, however, is acceptable to only 50% of the patients due to late tumor detection and early extramural spread of unresectable cancers or radiographically visible metastases at the time of diagnosis of esophageal cancer.[3,4] Treatment, therefore, focuses mainly on palliation therapy of dysphagia and odynophagia, employing a stent to mechanically open a blocked esophagus, thereby allowing feeding capacity and improving quality of life.

Various types of esophageal stents, made of metal, plastic or bioabsorbable polymer, have been technically evolved[5-8] and many of them are already in clinical use to relieve dysphasia.[5,6] These stents are designed to possess good mechanical flexibility for ease of insertion and elimination of excessive esophagus dilation.[5,7] However, for almost all cases, the esophageal stents suffer from re-occlusion due to rapid growth of tumors around the stent to shorten the effective lifespan of the treatment, hence multiple of major surgeries for stent replacement.[5,6]

In this sense, local and sustained delivery of an anti-cancer agent would be advantageous to suppress the tumor growth around the esophageal stent. In such systems, the drug would be released specifically towards the cancerous tissues in the esophagus, possibly achieving effective drug bioavailability around a stent for a prolonged period of time without unnecessarily high systemic drug exposure. However, to our knowledge, the esophageal stents enabled with delivery of an anti-cancer drug have not been widely studied, as compared with the other different types of drug-eluting stents, such as vascular stents.[9,10]

Recently, the esophageal stents were coated with biocompatible polymers, such as ethylene-vinyl acetate (EVA) and silicone, as a delivery medium for an anti-cancer drug,[11-13] which could release the drug in a sustained pattern for a prolonged time, achieving high drug bioavailability near the site of action and thus, alleviating restenosis. In spite of those potential advantages, the coating process employed for the above-mentioned stents may still have room for

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improvement since it was a multi-step procedure, composed of separate fabrication of each of the individual drug-delivery layers and assembly of the resulting layers and a stent. For example, for the stent coated with a drug loaded silicone layer, the layers were prepared separately on a jig of the shape of a stent, which were isolated from a jig, and then assembled and bonded with a stent.[11] The EVA-coated stent also needs assembly of a drug-loaded polymeric layer, which was again prepared separately, and a stent, where a heat and pressure were applied for their bonding.[12,13] Especially for the assembly procedure, a manual process may be needed to align and bond the layer on a stent properly.

In this sense, the electrospinning method may benefit from easy coating of an esophageal stent with drug-loaded biocompatible polymer. Simple electrospinning of a solution of drug and polymer could prepare the coated layers on top of a stent without any additional procedures. Nanofibers of drug-loaded polymer would be deposited almost in a dry form, which might also decrease the time for solvent removal. For this reason, many different stents other than an esophageal stent were successfully coated with drug or polymer.[14,15]

In this work, we coated an esophageal stent with the electrospinning method, employing poly(lactic-*co*-glycolic acid) (PLGA) and 5-fluorouracil (5-FU) as a polymeric coating layer and a model anti-cancer drug, respectively. 5-FU is widely used for treatment of cancers of the aerodigestive and esophageal tracts, which is known to inhibit the nucleotide synthetic enzyme, thymidylate synthase, that is necessary for DNA replication and repair, causing cell cycle arrest and apoptosis.[16] PLGA is known to be highly biocompatible, degrading into lactic and glycolic acids, which are common metabolites found in the body.[17]

We coated the esophageal stents with three different layers composed of drug-loaded PLGA nanofibers (DPN) and PLGA nanofibers only (*i.e.*, PLGA nanofibers without the drug) (PN). Thus, the stents were coated with the DPN layer only, or the PN layers were additionally coated over the DPN layer to better control drug release. We varied the collection time of PN layers to 0, 60, and 90 min to give the three differently coated stents (*i.e.*, DPNS1, DPNS2, and DPNS3, respectively) in this work. For DPNS1, only the DPN layer was coated on a stent, where PLGA nanofibers themselves served as a wall material to sustain drug release. For DPNS2 and DPNS3, the PN layers on top of the DPN layer worked as an additional rate-limiting barrier, where the drug release profiles could be varied according to the thickness of PN layer.

Experimental

Materials. Poly(lactic-*co*-glycolic acid) (PLGA; 50:50; lot number LX00195-116; *i.v.*=0.46 dL·g^{-1}; average MW= 42,000) was obtained from Lakeshore Biomaterials (AL, USA). 5-FU was purchased from Sigma (MO, USA). Dichloromethane (DCM), tetrahydrofuran (THF) and dimethylformamide (DMF) were obtained from JT baker (NJ, USA), Daejung (Korea) and Mallinckrodt (MO, USA), respectively. Phosphate-buffered saline (PBS; pH 6.5) was obtained from Seoul National University Hospital Biomedical Research Institute. Esophageal stents (E02010) were a kind gift from Tae Woong Medical (Korea).

Preparation of Coated Esophageal Stents. The esophageal stents were coated with PLGA nanofibers loaded with an anti-cancer drug, 5-FU by the electrospinning method. First, 600 mg PLGA or a blend of 600 mg PLGA and 18 mg 5-FU was dissolved in a 2 mL solvent mixed with DCM, THF, and DMF (3:1:1=v/v/v) to give a PLGA solution or a 5-FU and PLGA solution (the initial drug loading of 3% w/w),[18] respectively. The resulting solution was electrospun on top of the stents under the following conditions (Nano NC, Korea): applied voltage: 20 kV, collector distance: 10 cm, flow rate: 0.6 mL·h^{-1}, rotation speed of an esophageal stent: 1,000 rpm.

The stents were coated to possess three different layer properties, giving DPNS1, DPNS2, and DPNS3. To prepare DPNS1, a PLGA and 5-FU solution was electrospun for 30 min to prepare a DPN layer only. To prepare DPNS2 and DPNS3, a PLGA solution was first electrospun for 60 and 90 min, respectively, then a PLGA and 5-FU solution for 30 min, and a PLGA solution for another 60 and 90 min, respectively. In this way, both top and bottom of a DPN layer could be completely covered by additional PN layers for both DPNS2 and DPNS3. The resulting layers were then lyophilized under high vacuum for more than 48 h in order to remove any residual solvent.[19]

Scanning Electron Microscopy (SEM). A nanofiber layer was detached from the stents and cut into a 5 mm×5 mm piece, which was then placed on a SEM sample mount and sputter coated with platinum for 10 min (208HR, Cressington Scientific, England). The sample was then imaged by SEM (7501F, Jeol, Japan).

X-ray Diffraction Pattern (XRD). Crystallinity of PN and DPN was examined by an X-ray diffractometer (D/MAX RINT 2200-Ultima, Rigaku, Japan) equipped with Ni-filtered CuK_α radiation (λ=1.5418 Å). The samples were deposited on a glass substrate and continuously scanned at the tube voltage and the current of 40 kV and 30 mA, respectively.[20] The 5-FU and intact PLGA were also analyzed for comparison.

Thermal Analysis. A differential scanning calorimetry (DSC, DSC2910, TA instruments, DE, USA) was performed to examine the thermal properties of PN and DPN. A piece of a PN or DPN layer (each 7.5 mg) was placed in a hermetic pan under nitrogen gas flow, where the temperature was raised from 0 to 150 °C at a rate of 5 °C·min^{-1}, and then cooled at the same rate. This cycle was repeated five times to confirm the reproducibility.

Determination of Drug Content. The coated layers on

DPNS1, DPNS2, and DPNS3, each detached from the stents, were cut into a 1 cm×1 cm piece and then completely dissolved in 1 mL DCM. After that, 14 mL of phosphate buffered saline (pH 6.5) was added to the resulting solution, which was sonicated at 80 W for 5 min (Model 500 Digital Sonic Dismembrator, Fisher Scientific, PA, USA) and centrifuged at 4,800 rpm for 30 min at 20 °C (Allegra 21R, Beckman, CA, USA). The supernatant was taken and analyzed by high performance liquid chromatography (HPLC, Agilent 1100 series, Agilent Technologies, CA, USA) using a Zorbax® C18 column (4.5 mm×25 mm, 5 μm; Agilent Technologies, CA, USA). The mobile phase was prepared by mixing an aqueous solution of 0.02 M phosphoric acid and methanol (98:2; v/v). The flow rate and injection volume were 0.8 mL·min^{-1} and 10 μL, respectively. The column temperature was maintained at 20 °C and the UV absorbance was measured at 265 nm.

***In vitro* Degradation Study.** To examine the *in vitro* degradation profiles, the coated layers of DPNS1, DPNS2, and DPNS3, each detached from the stents, were cut into a 1 cm ×1 cm piece and their initial weights were measured. Each of the samples was then placed in 2 mL of an aqueous medium buffered at pH 6.5 and incubated at 37 °C for 3 weeks. At scheduled intervals, the samples were taken out, washed thoroughly with DI water and freeze-dried for more than 2 days. The weights of the resulting samples were measured and compared with their initial weights.

***In vitro* Drug Release Test.** The coated layers from DPNS1, DPNS2, and DPNS3, each detached from the stents, were cut into a 1 cm×1 cm piece, which was then immersed in the aqueous media buffered at pH 6.5 at 37 °C. The aliquot of the release media was sampled at scheduled intervals and assayed with HPLC as described above. The experiments were performed in triplicate for statistics.

Results and Discussion

Characterization of Coated Esophageal Stents. In this work, we coated the stents with drug-loaded polymeric layers for their potential application to local and sustained delivery of an anti-cancer drug around the esophagus. For this purpose, we employed PLGA and 5-FU as a wall material and a model anti-cancer drug, respectively, which were electrospun to deposit nanofiber layers on top of a stent. Figure 1 shows the optical images of the esophageal stents before and after coating. A bare stent used in this work (E0210, Taewoong Medical, Korea) was braided with nitinol wire to give mechanical flexibility for ease of insertion. The flanges were formed at both proximal and distal ends to avoid stent migration,[21] which were 28 mm in diameter and 15 mm in length. The body part of a stent was 20 mm in diameter and 70 mm in length. Figure 1(b) shows a representative image of the stent coated with nanofiber layers of PLGA loaded with 5-FU (*i.e.*, DPNS1), revealing that the

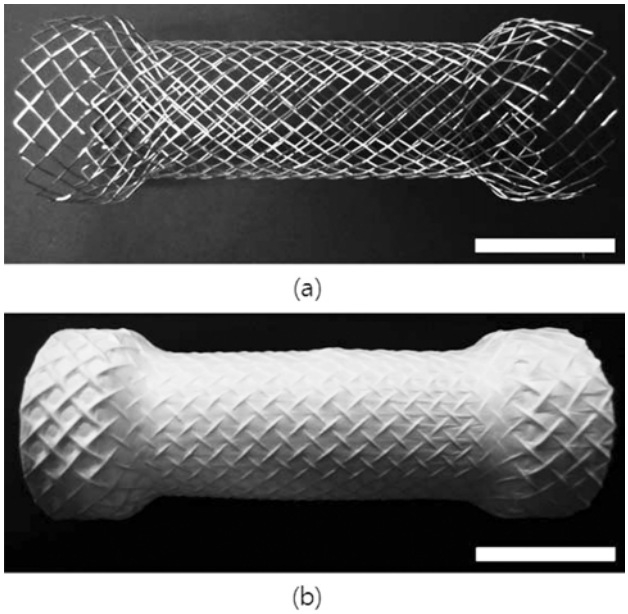

Figure 1. Representative optical images of (a) a bare esophageal stent and (b) an esophageal stent coated with DPN. The scale bars were 20 mm.

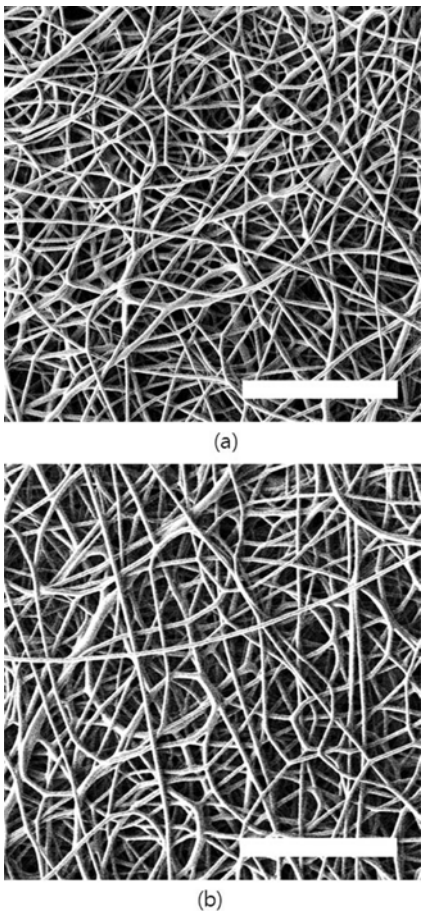

Figure 2. Scanning electron micrographs of (a) PN and (b) DPN. The scale bars were 50 μm.

Table I. Layer Compositions and Thicknesses of Nanofiber Layers Coated on the Stents

Layer Type	Layer Composition[a]	Thickness (μm)
DPNS1	PN (inner)	0±0.0
	DPN (middle)	70±1.6
	PN (outer)	0±0.0
DPNS2	PN (inner)	134±1.0
	DPN (middle)	54±0.7
	PN (outer)	98±1.0
DPNS3	PN (inner)	192±1.1
	DPN (middle)	47±0.7
	PN (outer)	122±0.6

Values are mean±SD. [a]The inner PN layer is located on the very top of the stent and the outer layer is on the very outside of the three layers of PN, DPN, and PN. The DPN layer is sandwiched between two distinct PN layers.

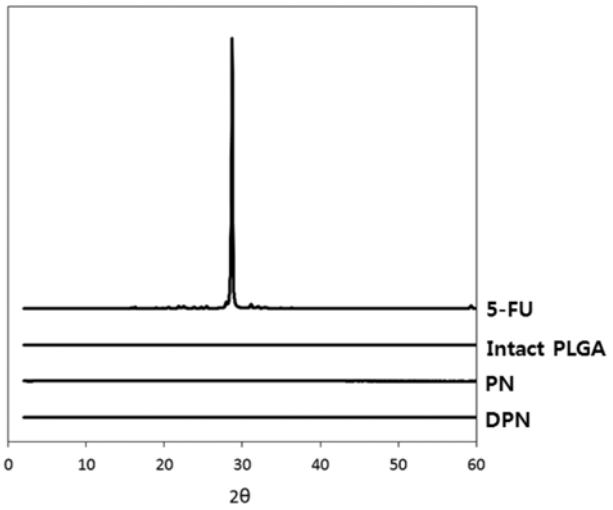

Figure 3. X-ray diffraction patterns of 5-FU powder, intact PLGA, PN, and DPN.

stent could be seamlessly coated with the electrospinning method employed in this work. Regardless of the presence of 5-FU, the electrospun layer of PLGA exhibited an apparent nanofibrous structure, as shown in Figure 2.

To control drug release, we coated the stents with three different types of nanofiber layers to give DPNS1, DPNS2, and DPNS3, respectively (Table I). The DPNS1 was prepared by electrospinning a solution of PLGA and 5-FU to coat a stent with a DPN layer (*i.e.*, a layer with PLGA and the drug) only. For DPNS2 and DPNS3, a PLGA solution was first electrospun to coat a stent with a PN layer (*i.e.*, a layer with PLGA only), on top of which a DPN layer was coated and then, a PN layer was coated again over the top of a DPN layer. In this way, an additional diffusion barrier could be formed around a DPN layer for both DPNS2 and DPNS3. The times for coating each of the layers were 0 min PN; 30 min DPN; 0 min PN and 60 min PN; 30 min DPN; 60 min PN and 90 min PN; 60 min DPN; 90 min PN for DPNS1, DPNS2, and DPNS3, respectively. The average thicknesses of the resulting layers were 0 μm PN; 70 μm DPN; 0 μm PN and 134 μm PN; 54 μm DPN; 98 μm PN and 192 μm PN; 47 μm DPN; and 122 μm PN for DPNS1, DPNS2, and DPNS3, respectively (Table I).

Notably, although the DPN layers were deposited during the same time period (30 min) for all stents, the thickness of DPN layer decreased as the thickness of the inner PN layer on top of a stent increased. This could be ascribed to the electric insulation formed by the PN layer first deposited on a stent,[22] which appeared to reduce the electric field strength as the thickness of the PN layer increased. For the same reason, the outer PN layer deposited on top of the DPN layer was thinner than the inner PN layer initially deposited on top of a stent although both PN layers were collected during the same time period (Table I).

Characterization of Coating Layers. Figure 3 shows the XRD patterns of 5-FU, intact PLGA, PN, and DPN. 5-FU exhibited a crystalline peak at $2\theta=28^{o}$, while intact PLGA and PN were amorphous with no crystalline peaks.[20,23] However, even with the presence of 5-FU, the DPN showed no XRD peaks, suggesting that the 5-FU molecules were homogeneously distributed in the DPN layer without forming an evident crystalline structure. Figure 4 shows the results from DSC analysis of 5-FU, intact PLGA, PN, and DPN. T_g of intact PLGA was obtained at 48.1 °C, which was lowered to 38.2 °C with the PN. The decrease in T_g could be ascribed to a large surface to volume ratio of the PLGA nanofiber layers embedded with air as a plasticizer,[24] increasing the spacing and free volume in nanofibers, thereby more flexibility of the polymer chains.[25] T_g did not vary much with the

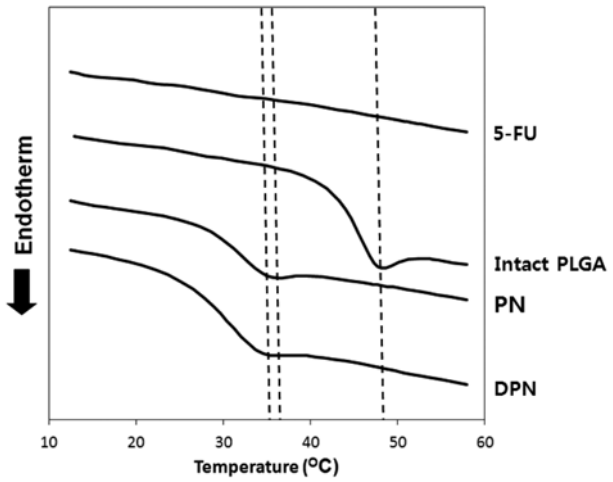

Figure 4. Differential scanning calorimetry thermograms of 5-FU powder, intact PLGA, PN, and DPN. The dashed lines indicate T_g of intact PLGA, PN, and DPN.

Table II. Drug Loading Amounts and Efficiencies in Nanofiber Layers Coated on the Stents

Layer Type	Thicknesses of DPN (μm)	Drug Amount (μg per cm^2)	Drug Amount[a] (μg per cm^2)	Drug Loading Efficiency[b] (%)
DPNS1	70±1.6	15.66±0.76	15.66	72.9
DPNS2	54±0.7	12.42±0.29	16.10	74.9
DPNS3	47±0.7	10.62±0.27	15.82	73.6

Values are mean±SD. [a]The drug amounts per cm^2 were calculated, assuming the same thickness of the collected DPN layers (70 μm). [b]The drug loading efficiency was calculated in percentage by dividing the actual loading amount in nanofibers by the initial loading amount.

DPN as compared with the PN but slightly lowered to 36.8 °C, which might be ascribed to the presence of 5-FU.

Table II shows the loading amounts of 5-FU per cm^2 of each of the coating layers from DPNS1, DPNS2, and DPNS3. The drug loading amounts decreased as the thickness of additional PN layers increased, which was somewhat expected since the thickness of a DPN layer decreased with the presence of a PN layer. As described above, the addition of the PN layer resulted in insulation to cause reduction in electric field strength, thereby a decrease in total amount of the collected DPN nanofibers. Thus, the average loading amounts of 5-FU were 15.66, 12.42, and 10.62 μg per cm^2 for DPNS1, DPNS2, and DPNS3, respectively. Where a DPN layer of the same thickness was assumed to be collected, the drug amounts per cm^2 should not be very different for all coated stents, as shown in Table II. Thus, the drug loading efficiencies were 72.9%, 74.9%, and 73.6% for DPNS1, DPNS2 and DPNS3, respectively.

***In vitro* Degradation of Coating Layers.** We examined *in vitro* degradation behaviors of nanofiber layers from DPNS1, DPNS2, and DPNS3 by measuring the change in remaining amount after immersion in the aqueous media at pH 6.5, mimicking the biological fluid at the esophagus.[26] Figure 5 shows the remaining amount percent of the coating layers from each of the stents prepared in this work, all of which exhibited an apparent decrease in their remaining amount. The degradation of DPNS1 layer seemed to be relatively faster, especially for the first 2 days, than that of DPNS2 and DPNS3 layers, which could be attributed to rapid drug release *via* the DPN layer, leaving the pores on the layer to give a large surface area interacting with the surrounding medium. On the other hand, the additional PN layers seemed to prevent this rapid pore formation for DPNS2 and DPNS3, hence relatively slower degradation. After 21 days of immersion, the remaining amount decreased to 62%, 68%, and 68% for DPNS1, DPNS2, and DPNS3, respectively.

***In vitro* Drug Release Profiles.** We examined the *in vitro* release profiles of 5-FU with the coating layers, each detached from DPNS1, DPNS2, and DPNS3, respectively. As shown in Figure 6, almost 70% of the drug was released from the DPNS1 layers during the first day, which was completed in 6 days. This rapid release could be due to a hydrophilic nature of 5-FU, which is known to be highly soluble in the aqueous media (~12.5 $mg \cdot mL^{-1}$),[27] and thus, a

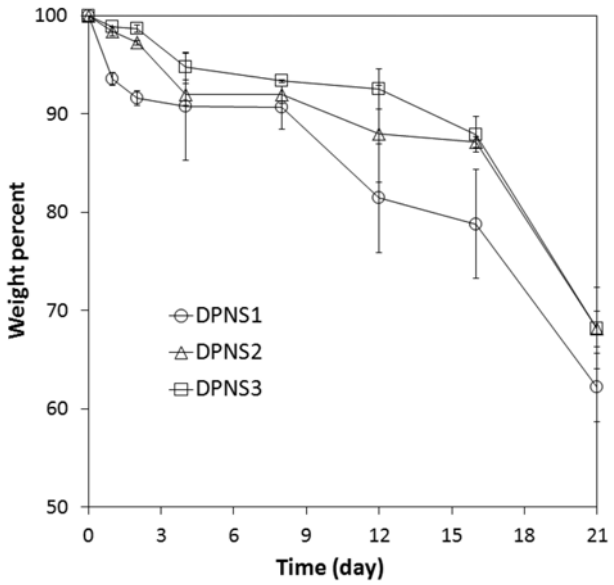

Figure 5. Weight percent of the remaining nanofiber layers from DPNS1, DPNS2, and DPNS3 after degradation to their initial weights.

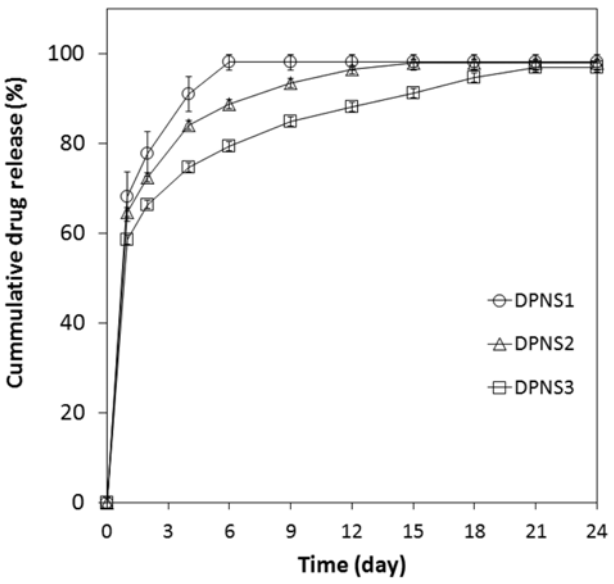

Figure 6. *In vitro* release profiles of 5-FU from DPNS1, DPNS2, and DPNS3.

release pattern appears to be not determined by polymer degradation but be controlled mostly *via* drug diffusion. To prolong drug release, therefore, we added the PN layers as an additional diffusion barrier. As a result, the layers from DPNS2 and DPNS3 continued drug release on 6 days, still containing about 11.3% and 21.7% of the drug remaining in the layers, respectively and thus, drug release was also more sustained as the thickness of the PN layer increased. A period of drug release was extended to 15 and 21 days for DPNS2 and DPNS3, respectively.

An esophageal stent is accepted in clinical use to mechanically open an esophagus clogged by cancerous tissues, allowing feeding capacity as well as improving a life quality of the patients.[5,6] Various types of esophageal stents have been developed for this purpose,[5-8] many of which, however, still pose problems of re-occlusion due to rapid growth of tumors around the stent. This reduces the effective lifespan of the stent, needing multiple times of major surgeries for stent replacement.[5,6]

To resolve this, the esophageal stents enabled with local delivery of an anti-cancer drug have been developed by coating the surface of the stents with biocompatible polymers, such as ethylene-vinyl acetate (EVA) and silicone.[11-13] This coated layers of polymer were loaded with an anti-cancer drug, where a drug could be released in a sustained manner over a prolonged period of time, achieving high drug bioavailability around the stent and thus, alleviating restenosis.

Inspired by those previous results, we coated a stent with the electrospinning method to prepare a nanofiber layer of a biocompatible polymer, PLGA, on top of a stent,[17] where an anti-cancer drug, 5-FU, was loaded to be released in a sustained manner (Figure 1). In the coating layers, the drug was seen to be homogeneously distributed in a molecular level (Figure 3), suggesting that local toxicity of an anti-cancer drug, 5-FU, possibly caused by crystallized drug particulates in the layer, be highly improbable. After complete drug release, the PLGA nanofiber layers should be biodegraded into lactic acids and glycolic acids, which are common metabolites found in the body, to disappear eventually (Figure 5).

However, the stents coated with this single layer composed of the polymer and drug (*i.e.*, the DPN only) was limited in a relatively short period of drug release only for 6 days (DPNS1). To further control drug release, therefore, we coated the stents with the multi-layered nanofibers composed of drug-loaded polymer (*i.e.*, DPN) and polymer only (*i.e.*, PN). In this work, we added the PN layers surrounding the DPN layer as an additional diffusion barrier. Thus, the DPN layer was sandwiched with two distinct PN layers. As a result, drug release could be more prolonged for up to 21 days (DPNS3) as the thickness of PN layer increased (Figure 6). Considering about 100 days of a median survival period of patients with esophageal cancer after stent placement,[28] we envision that the period of drug release can be optimized by simply varying the thickness of the PN layers as a more resistive diffusion barrier.

The electrospinning method employed for coating the esophageal stents in this work could benefit from a simple fabrication procedure. Previously, to coat the stents with drug-delivery layers, each of the coating layers was separately prepared, which was then assembled manually with a stent, employing a solvent or heat for their attachment.[11-13] With the electrospinning method, the nanofibers of drug-loaded polymer were directly deposited on top of a stent to form a layer enabled with drug delivery. Therefore, the coated stents would not need any additional procedures except for complete evaporation of the solvent utilized to prepare a drug and polymer solution for electrospinning. However, a short drying time is expected since nanofibers generated by electrospinning would not generally contain much of residual solvent. Moreover, a large area of nanofiber layers have been successfully fabricated with the electrospinning method,[18] which would be favorable for coating of multiple stents at once in a scale up production. In this way, the thicker PN layers employed for a prolonged drug release could be obtained simply by a longer collection of PN nanofibers *via* electrospinning. The stability of 5-FU is expected to be retained during this process since the organic solvents and a high voltage used for electrospinning were reported to have almost no effect on the drug activity.[1,29]

The coating layers that we prepared in this work may need to be improved further to give more mechanical flexibility and pliability needed for a practical use of an esophageal stent. For example, the stent needs to be contracted for insertion, which is then expanded fully after placement in the esophagus.[30] In addition, the stent is usually under repetitive mechanical stress due to the peristalsis of esophagus.[29] To be more acceptable, therefore, the coating layers may need to be composed of more pliant polymers, such as elastomers.[31] Incorporation of a plasticizer, such as polyurethane and poly(lactic-*co*-ε-caprolactone) may also help to give more flexibility to the PLGA coating layers.[32] The study is now in progress to develop the esophageal stents coated with the polymeric layers with more flexibility, as well as longer drug release.

Conclusions

An esophageal stent has been accepted in clinical use for palliative therapy to relieve malignant dysphagia and odynophagia mostly found with the esophageal cancer patients. However, many of the stents are still limited in restenosis due to rapid growth of tumor cells around the stent. To address this obstacle, we developed the esophageal stents enabled with delivery of an anti-cancer drug. For this purpose, the stents were coated with nanofiber layers of a biocompatible polymer, PLGA, containing an anti-cancer drug,

5-FU, *via* electrospinning. A coating procedure with the electrospinning method is considered to be simple, as compared with some of the previous trials involved with separate fabrication of drug-delivery layers and manual attachment of the layers to a stent.

The stents coated with drug-loaded nanofibers (DPN) can sustain drug release and the period of drug release can be more prolonged by adding nanofiber layers composed of PLGA only (PN), surrounding the DPN layer, as a more resistive diffusion barrier. The stents coated with a 70 μm-thick DPN layer in this work could release the drug for 6 days, which could be extended to up to 21 days when the 122 and 192 μm-thick PN layers were deposited on top and bottom of the DPN layers, respectively. We expect that a longer drug release period can be realized simply by incorporating the thicker PN layers *via* electrospinning. Therefore, we conclude that a drug-delivery esophageal stent suggested in this work has a promising potential for a long-term treatment of dysphagia of the esophageal cancer patients.

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