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Role of silica nanoparticles in monitoring and prolonging release of drug-eluting polyelectrolyte coatings using long-period fiber grating platform

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ABSTRACT

Silica nanoparticles (SNPs) were synergistically integrated with long-period grating (LPG) platform and the process of layer-by-layer (LbL) assembly to enable monitoring controlled release of drug-eluting polyelectrolyte coatings. The SNPs afforded a high surface area for increased drug loading as well as enhanced evanescent field overlap. In addition, the SNPs positioned within the LbL coatings acted as diffusion barrier layer, leading to prolonged release profile. SNPs with different sizes were respectively immobilized on the LPG using poly allylamine hydrochloride (PAH). In-situ monitoring of drug-eluting LbL coating [chitosan (CHI)/Poly arylic acid (PAA)/Gentamicin sulfate (GS)/PAA]$_n$ was carried out on LPG with a sensitivity of 8.1 nm shift/tetralayer for LPG with 1 layer of SNPs with 50 nm in diameter. LPG without the SNPs for the monitoring of [CHI/PAA/GS/PAA]$_n$ shows a sensitivity of 2.4 nm shift/tetralayer, indicating the significant ability of SNPs in enhancing the LPG sensitivity. Drug release measurement carried out on the LPG platform revealed an increased release time for LbL-SNP drug delivery system compared with that of LbL alone.

1. Introduction

Biocompatible and biodegradable therapeutic-eluting polyelectrolyte polymer films via layer-by-layer (LbL) assembly hold significant promise as functional coatings on medical implants and tissue scaffolds of complex shape and geometry for patient care. Examples include prevention of bacterial infection in the implant region through localized release of antibiotics and promotion of tissue integration of the scaffold by a steady supply of growth factors, among other utilities [1]. For instance, hydrolytically degradable LbL polyelectrolyte coatings on titanium implant and 3D-printed macroporous scaffolds respectively loaded with antimicrobial drug [2] and bone tissue growth factor [3] were shown to exhibit the efficacy in treating infection and promoting tissue growth using animal models. The incorporation of drugs in LbL coatings at physiologically relevant doses remains very challenging, however. For example, microgram doses of biologics necessary for directing host tissue response have been very difficult to achieve using the LbL strategy alone [3].

The development of the LbL polyelectrolyte thin films has been facilitated by robust photonic techniques such as surface plasmon resonance [4,5], whispering gallery mode [6], fiber optic sensors [7–10], and photonic crystal resonator arrays [11]. The ability to study the LbL process and the responsiveness of the polyelectrolyte films is critical from the point of view of coating design and performance. Long-period grating (LPG) structure offers such a capability by virtue of its high refractive index sensitivity [12–14] and the feasibility for thin film growth in the cladding area of the fiber. Compared to the other thin film measurement techniques such as quartz crystal microbalance, absorption spectroscopy and ellipsometry, LPG provides easy in-line integration for measurements in real time and shall prove powerful platform for design and evaluation of drug-eluting LbL polyelectrolyte coatings.

Silica nanoparticles (SNPs) have shown to be significant enablers for a variety of applications due to their unique physicochemical, mechanical and optical properties [15,16]. For example, they can self-organize into an ordered structure, serving as template for inverse opal photonic bandgap structure [17,18]. Mesoporous nanostructured silica thin film with high porosity and surface area

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has been extensively investigated for sensing humidity or volatile organic chemicals [19]. Because of the well-define structure and excellent biocompatibility, SNPs are being increasingly incorporated into biological and biomedical systems [20–30], including controlled drug delivery and release. Porous SNP coatings deposited on LPG were shown to improve the sensitivity for ammonia chemical sensing [31]. The deployment of SNPs allowed for the freedom in the design of LbL drug delivery platform for the systemic co-delivery of an anticancer drug and siRNA for treatment of triple-negative breast cancer [32].

Significant potential thus exists in the synergistic integration of SNPs with LPG and LbL for in-situ investigation of improved drug loading and controlled release. Here we explore and demonstrate this potential using a model polyelectrolyte coating system with [CHI/PAA/GS/PAA] tetralayer as a building block, where CHI, PAA and GS represent chitosan, polyacrylic acid and gentamicin sulfate (the antibiotic drug), respectively. SNPs were deposited onto the grating portion of the LPG to 1) enlarge the surface area of the substrate onto which the tetralayer will be deposited, 2) tune the evanescent field overlap of the cladding mode in the grating vicinity to promote high sensitivity and 3) modulate release properties in the subsequent drug release measurement as a two-dimensional barrier layer. A set of parameters including particle size and layer number was explored in the investigation of their effect on the monitoring of drug-eluting polyelectrolyte deposition. To evaluate the effect of the barrier layer, in situ drug release measurements were taken and compared for LPGs with, without SNPs coating, as well as for cases where a number of SNPs layers were deposited at different locations within the drug delivery thin film. Theoretical calculation was carried out to analyze the mode field for LPG with the SNP coatings (SNPs/LPG). The effect of nanoparticles size on the monitoring of LbL deposition was also studied.

2. Methods and experiments

2.1. Materials

Poly(acrylic acid) (PAA, Mw ~ 450 kDa), Chitosan (CHI, Mv ~ 60–120 kDa), 3 M sodium acetate buffer (NaOAc, pH 5.2), Poly(allylamine hydrochloride) (PAH, Mw ~ 17,000), were purchased from Sigma-Aldrich (St. Louis, MO). Gentamicin sulfate (GS) was purchased from Mediatech, Inc. (Herndon, VA). Single mode fiber SMF 28 was purchased from Corning, Inc. (Corning, NY). Silica nanoparticles were purchased from nanoComposix, Inc. (San Diego, CA).

2.2. Fabrication of LPG

LPG refers to the periodic index perturbations typically hundreds of microns in periodicity on the optical fiber. It couples the fundamental core mode to co-propagating cladding modes, if the phase matching condition $\lambda_{resonance} = (n^{eff,}{}_{core} - n^{eff,}{}_{cladding})\Lambda$, is satisfied [33], where $n^{eff,}{}_{core}$ and $n^{eff,}{}_{cladding}$ are respective effective indices of the core and the cladding modes, $\lambda_{resonance}$ is the resonance wavelength of the coupled cladding mode, and Λ is grating period. The strong dependence of $\lambda_{resonance}$ on $n^{eff,}{}_{cladding}$ makes LPG a highly sensitive index transduction platform for sensing applications. The sensitivity of the LPG increases with the increase of the order of coupled cladding mode. $LP_{0,10}$ cladding mode in the SMF 28 was selected for LPG coupling to achieve a high refractive index sensitivity [12]. CO_2 laser with 120° Au-coated Si mirror pair was used to fabricate the SMF-LPG with the period of 247 μm and length of 80 mm. The Si mirror pair turns the unidirectional beam into three beams 120° apart, achieving a symmetric inscription of SMF-LPG with higher reproducibility [34]. The CO_2 laser power for irradiation was 1.9 W and exposure time was 53 ms. The transmission spectrum of the as-fabricated SMF-LPG immersed in water is shown in Fig. 1(a). The theoretical calculation of the phase matching condition of the SMF-LPG was conducted based on Finite Element Method (FEM). Fig. 1(b) shows the phase matching curve (PMC) of $LP_{0,10}$ mode which relates the period to the resonance wavelength of the SMF-LPG. As can be seen from Fig. 1(b), the period of 248 μm gives rise to the coupling to $LP_{0,10}$ mode with a resonance wavelength of 1566 nm. The simulation results are close to the experimental results of 1558 nm in resonance wavelength with LPG period of 247 μm, and confirm that the LPG operates in a high sensitivity regime provided by $LP_{0,10}$ mode with a turn-around point (TAP) in PMC [7] nearby, as shown in Fig. 1(b). New LPG is used for each of the measurements. Due to the slight variation in LPG fabrication conditions (such as power fluctuation of the CO_2 laser), the resonance wavelengths of the fabricated LPGs are not exactly the same. Before each of the measurements, the LPGs were cleaned by subsequently rinsing with ethanol, DI water, H_2O_2 (10 wt% in water) and DI water.

2.3. Preparation of polyelectrolyte solutions

Dipping solutions of CHI and PAA were prepared at 2 mg/mL in 100 mM sodium acetate buffer and pH adjusted to 5.0. The dipping solution of GS was at 10 mg/mL in 100 mM sodium acetate buffer. PAH solution was prepared at 0.2 mg/mL in milliQ water and pH adjusted to 9.0. SNPs was diluted from 10 mg/mL to 2 mg/mL using milliQ water and pH adjusted to 5.2. SNPs were negatively charged in the pH of 5.2 as confirmed by the zeta-potential measurement of −56.5 mV.

2.4. Layer-by-layer film formation on SMF-LPG

The SMF-LPG was dipped into a container with a V-groove holding the polymer and SNPs solutions during the LbL deposition until the desired number of tetralayer was achieved on the SMF-LPG platform. SNPs were deposited onto SMF-LPG by alternately dipping in a solution of cationic PAH for 20 min followed by consecutive three rinse steps and then into anionic SNP solution for 1 h followed by another three rinse steps. Drug delivery tetralayer films were fabricated at room temperature by alternate dipping in a solution of cationic species for 10 min followed by three consecutive rinse steps in 100 mM sodium acetate baths, and then into anionic species for 10 min followed by the same rinse cycle. The entire cycle was repeated until the desired number of tetralayers was deposited. The transmission spectra of SMF-LPG were obtained during the course of deposition to monitor the SNPs and LbL growth in situ.

2.5. Drug release measurement

During the drug release measurement, the LPG coated with $[CHI/PAA/GS/PAA]_n$, where n is the number of tetralayers, were immersed in the phosphate-buffered saline (PBS) at pH 7.4 with temperature maintained at 37 °C in a water bath. The GS release profiles were obtained in situ by tracking time-dependent resonance wavelength shift in light transmission in LPG using a super-K ultra broadband supercontinuum light source and optical spectrum analyzer (OSA, Anritsu MS9710C). More details can be found in ref [35].