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In-Situ Monitoring of Drug Release from Therapeutic Eluting Polyelectrolyte Multilayers under Static and Dynamic Conditions

Fei Tian^{*a}, Jouha Min^{b,c}, Jiri Kanka^d, Paula T. Hammond^{b,c}, Henry Du^a

^aDepartment of Chemical Engineering and Materials Science, Stevens Institute of Technology, Hoboken, NJ 07030, USA

^bDepartment of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

^cDavid H. Koch Institute for Integrative Cancer Research, Cambridge, MA 02139, USA

^dInstitute of Photonics and Electronics AS CR, v.v.i., Chaberska 57, Prague 8 18251, Czech Republic

[*ftian1@stevens.edu](mailto:ftian1@stevens.edu)

ABSTRACT

The release profiles of gentamicin sulfate (GS) from [chitosan (CHI)/poly(acrylic acid) (PAA)/GS/PAA]_n polyelectrolyte multilayers were investigated in situ using an innovative lab-on-fiber (LOF) optofluidic platform that mimics physiologically relevant fluid flow in a microenvironment. The LOF was constructed by enclosing in a flow-enabled and optically coupled glass capillary a long-period fiber grating both as a substrate for LbL growth of [CHI/PAA/GS/PAA]_n and a measurement probe for GS release. We show that the LOF is very robust in monitoring the construction of the [CHI/PAA/GS/PAA]_n multilayers at monolayer resolution as well as evaluating the rate of GS release with high sensitivity. The release processes in the LOF under static and a range of dynamic conditions are evaluated, showing a faster release under dynamic condition than that under static condition due to the varying circumstance of GS concentration gradient and the effect of flow-induced shear at the medium-multilayer interface. The LOF platform has the potential to be a powerful test bed to facilitate the design and evaluation of drug-eluting polyelectrolyte thin films for their clinical insertion as part of patient care strategy.

Keywords: Long period grating, drug release, polyelectrolyte, thin film, dynamic, lab on fiber, gentamicin sulfate

1. INTRODUCTION

Layer-by-layer (LbL) is referred to as sequential alternating adsorption of polymer monolayers from solutions [1] by various molecular interactions including electrostatic attraction, hydrogen bonding, covalent cross-linking, among others [2-4]. Since its demonstration, LbL has been applied to a broad range of research fields. One of the most attractive fields is the controlled and targeted drug release. Therapeutic incorporation at significant doses in biocompatible and biodegradable LbL host and their controlled release under physiological conditions are at the frontier of the rapidly advancing LbL field [5,6]. A large body of literature exists that covers a diverse range of therapeutic agents such as small drugs [7], peptides [8,9], proteins [10,11] and nucleic acids [12] at mild aqueous conditions. LbL can be incorporated in the drug delivery structures in multiple ways. For example, Deng et al. have reported the study of the LbL integrated with nanoparticles for systemic codelivery of anticancer drug and siRNA for potential triple-negative breast cancer treatment [13]. In another study, Kim et al. designed a hydrogen bonded multilayer with polymetric micelles with tannic acid through LbL assembly for surface drug delivery [14]. Even more interesting, through careful design, LbL renders the freedom for the delicate release strategies at planned time scales for different type of therapeutic drugs. For example, Min et al. have demonstrated a tunable staged release of antimicrobial drug and bone growth factor from LbL coatings with clay interlayer barrier to achieve a fast release of gentamicin sulfate at the burst release stage for the elimination of the infection of bone implant site, followed by a clay-barrier-prolonged release of a bone-growth factor for the effective enhancement of the bone growth later on [15]. Eluting of drugs depends on many factors such as the physical and chemical properties of both the carriers and drugs in terms of chemical composition, porosity, surface roughness, degradation ability, molecular weight, particle sizes and interactions between drug and the delivering matrix. Different combinations of the above mentioned factors result in different drug release profiles and release mechanisms.

The investigation in the drug release profiles enables the analysis of the release mechanism and evaluation of the effectiveness in the disease treatment. Depending on the shape of the release profiles, there can be zero-order kinetics, first-order kinetics, mixed-order kinetics. Thus the study on the release profiles is of utmost importance to achieve proper functionalities for treatment effectiveness and eventually the clinic insertion.

The prevailing method to obtain the drug release profiles has been through the immersion of the drug delivery thin films in a sealed test tube with a fixed amount of releasing medium. The test tube is then immersed in the water bath for temperature control. The drug being released is measured by sampling the releasing medium at sequential time intervals and subjected to drug test using a variety of methods such as standard ELISA [16], radio-labels [17], or UV-Vis absorbance [18]. This static method, though helping to produce a large amount of information on the drug release profiles, does not take into consideration of the physiologically relevant conditions. For example, it is estimated that up to 20% of the body's mass is made up of interstitial fluid, and much of this fluid is in constant motion [19]. The typical interstitial flow rate in human is 0.1-2.0 $\mu\text{m/s}$ [20-22], which can be significantly increased under stress [19]. And dimension-wise, the commonly used osteoconductive scaffolds for bone graft have pore diameters ranging from 100 to 500 μm [23, 24].

Optical fiber based sensing platforms have been increasingly explored [25-29] due to its high speed, electric-magnetic field immunity, effective cost and compatibility. A long period grating (LPG) couples the light from the fundamental core mode to the co-propagating cladding mode where it is lost due to scattering and absorption. The phase matching condition is determined by $\lambda_{\text{resonance}} = (n_{\text{core}}^{\text{eff}} - n_{\text{cladding}}^{\text{eff}})\Lambda$, where, $\lambda_{\text{resonance}}$ is the coupling resonance wavelength of the cladding mode, $n_{\text{core}}^{\text{eff}}$ and $n_{\text{cladding}}^{\text{eff}}$ are respective effective indices of the core and the cladding modes, and Λ is grating period. The dependence of $\lambda_{\text{resonance}}$ on $n_{\text{core}}^{\text{eff}}$ and $n_{\text{cladding}}^{\text{eff}}$ makes LPG a sensitive index transduction platform. Indeed, robust LPG based sensing platforms have been demonstrated for a broad range of applications in gas sensing, bio-sensing and chemical sensing [30-38]. It is clearly an exciting candidate for the monitoring of the drug release profiles in real time.

In this study, we explore the influence of the physiologically relevant conditions on the drug release profiles of a model LbL [Chitosan (CHI)/ Polyacrylic acid (PAA)/ Gentamicin sulfate (GS)/PAA]_n tetralayer system in real time using a lab-on-fiber (LOF) platform [39]. The LOF platform is based on the LPG in single mode optical fiber (SMF). Different fluidic conditions are explored for the drug release profiles of the [CHI/PAA/GS/PAA]₁₀. By fitting the release data in a mathematical model, we show that there is a clear dependence of the release rate on the flow rate of the releasing medium. The influence of the thickness of the drug delivery thin film (or the tetralayer number) on the drug release process is also studied.

2. MONITORING OF THE LAYER-BY-LAYER DEPOSITION PROCESS

The SMF-28 is used for the fabrication of LPG with LP_{0,10} cladding mode coupled to achieve the optimized sensitivity. The fabrication is through symmetric irradiation of CO₂ laser assisted by a 120° angled mirror pair. The details for the symmetric fabrication can be found in [40, 41]. The resultant SMF-LPG has a period of 248 μm and a length of ~5 cm. The [CHI/PAA/GS/PAA]_n tetralayers are deposited on the LPG. CHI and PAA are purchased from SigmaAldrich (St. Louis, MO), and have a molecular weight of 60,000~120,000 Da and 450,000 Da, respectively. Gentamicin sulfate (GS) is purchased from Mediatech, Inc. (Herndon, VA). Phosphate buffered saline (PBS) are purchased from Invitrogen (Carlsbad, CA). Dipping solutions of CHI and PAA are prepared at 2 mg/mL in 100 mM sodium acetate buffer and pH adjusted to 5.0. The dipping solution of GS is at 10 mg/mL in 100 mM sodium acetate buffer. Figure 1 shows the chemical structure of the CHI, PAA and GS. They form tetralayer structure in the deposition solution through electrostatic interaction. The transmission spectra are recorded as each of the tetralayers is deposited on the SMF-LPG. Figure 2 shows the transmission spectra as the tetralayer is deposited with each tetralayer as a unit up to 3 tetralayers. The inset is the response of the SMF-LPG to the deposition of the [CHI/PAA/GS/PAA]_n tetralayers up to 10 tetralayers. It shows that there is a red shift as the layer is deposited, indicating an increase in the thickness of the thin film. According to the inset, there is a red shift as the 10 tetralayers are deposited. The results show that the SMF-LPG is very sensitive to the deposition of each of the tetralayers.

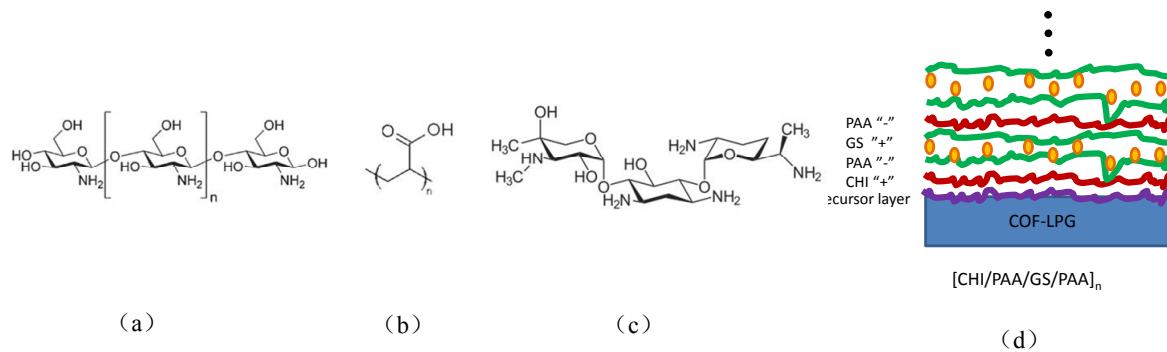


Figure 1. (a), (b) and (c) are chemical structures of CHI, PAA and GS, respectively; (d) tetralayer structure of $[CHI/PAA/GS/PAA]_n$ through electrostatic interaction.

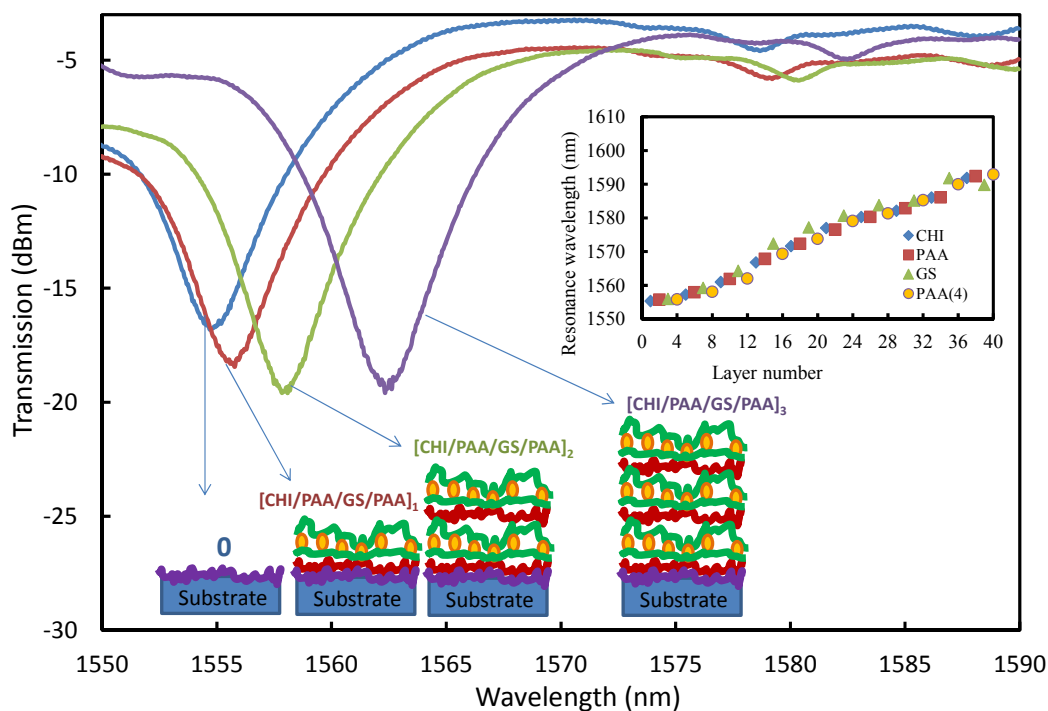


Figure 2. Transmission spectra of the SMF-LPG as the $[CHI/PAA/GS/PAA]_n$ is deposited up to 3 tetralayers. Inset is the response of the SMF-LPG to the deposition of the $[CHI/PAA/GS/PAA]_n$ up to 10 tetralayers.

3. MONITORING OF THE DRUG RELEASE PROFILES UNDER DIFFERENT FLUIDIC CONDITIONS USING LOF PLATFORM

The LOF platform used for the release measurement is composed of two components. The SMF-LPG serves both as a substrate onto which the coating is deposited and as a sensing element for the real time monitoring of the release process. Another component is a capillary tube hosting the coated SMF-LPG inside. It is connected with a micro pressure pump to provide the flow during release. At the meantime, it also ensures the light path through the SMF-LPG. The capillary tube with the SMF-LPG is then immersed in a water bath to keep the releasing temperature at 37 °C. Figure 3 (a) shows

the picture of the experimental setup including the light source, OSA, LOF, micro pressure pump and water bath. Figure 3 (b) shows the schematic of the LOF setup.

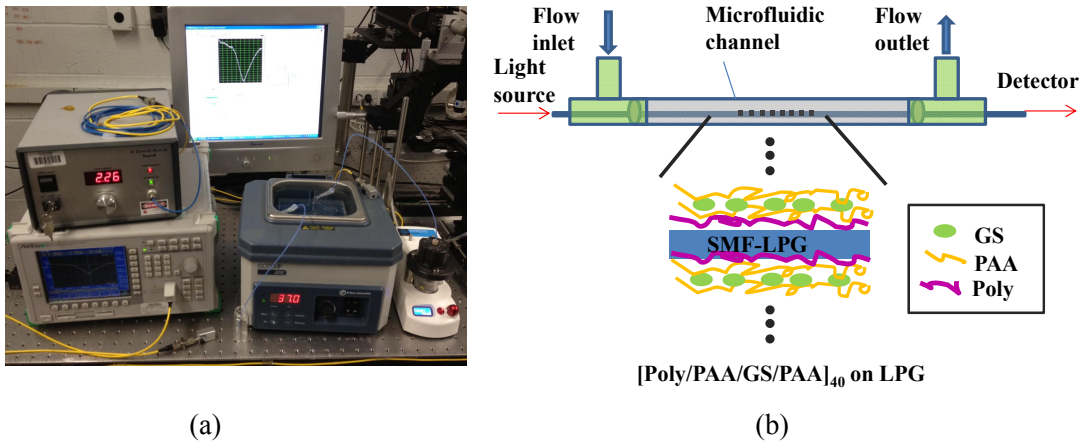


Figure 3. (a) Experimental setup and (b) schematic of the LOF platform.

To study the influence of flow rate on the release profiles, the drug release is studied under three fluidic conditions: static, 0.127 mL/min and 1 mL/min. The response of the SMF-LPG to the release process is recorded every 30 s for the first 30 min and then every 30 min up to 4 hours when the release is completed. Figure 4 shows the response of the SMF-LPG to the release of the GS as a function of time.

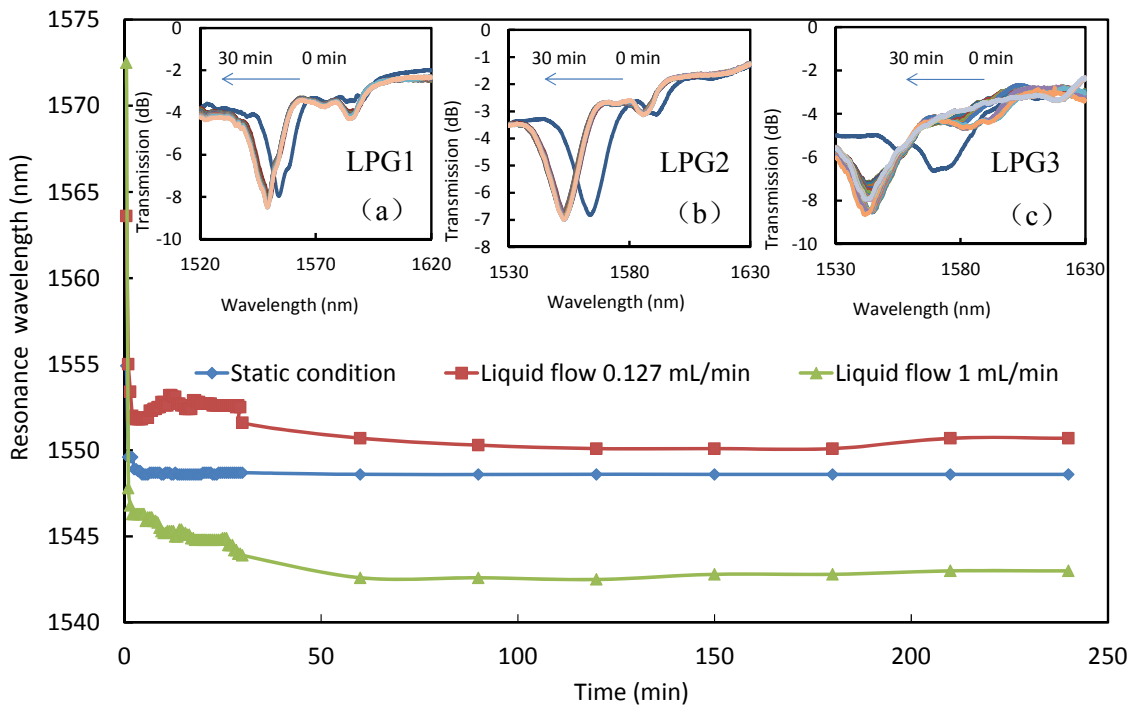


Figure 4. Response of SMF-LPGs to the release of GS under static, 0.127 mL/min and 1 mL/min conditions, respectively. Insets (a), (b) and (c) are the transmission spectra of LPG1, LPG2 and LPG3 under static, 0.127 mL/min and 1 mL/min conditions recorded at 1 min time interval, respectively.

Figure 4 shows that as the GS gradually releases from the [CHI/PAA/GS/PAA]₁₀ coating, there is blue shift in the resonance wavelength of SMF-LPG under static and each flow condition, indicating a decrease of the thickness of the coating as the GS releases from the matrix. To take a close look at the release mechanisms and the release rate, we use Peppas model to fit the experimental data. This model is most commonly used for the mathematical description of drug delivery kinetics. It is usually used for the study of the water-soluble drug release from polymer matrix [42]. The Peppas model is described by equation (1):

$$M = k \cdot t^n \quad (1)$$

where M is accumulative release in percentage, k is the release constant, t is the time for the release. It follows a time to the power of n relation. The release constant k is directly proportional to the diffusion coefficient D and depends on the structure and physical properties of both the drug and the polymer matrix. k is related to the release rate, and n can be used to characterize the release mechanism [42]. Table 1 shows the relationship between the number n and the release mechanisms under Peppas model. Table 2 shows the fitting parameters using Peppas model for all the three SMF-LPGs under static and each flow condition.

Table 1. Relationship between number n and the release mechanisms.

Release exponent n	Release Mechanism
Thin Layer	
$n \leq 0.5$	Fickian diffusion
$0.5 < n < 1.0$	Anomalous transport
$1.0 \leq n$	Case-II transport

Table 2. Fitting parameters for GS release from [CHI/PAA/GS/PAA]₁₀ coating under static and dynamic flow conditions.

Liquid flow	Static (LPG1)	0.127 mL/min (LPG2)	1 mL/min (LPG3)
	$y = 41 \cdot t^{0.28}$	$y = 34 \cdot t^{0.29}$	$y = 37 \cdot t^{0.30}$
k	41	34	37
n	0.28	0.29	0.30

Table 2 shows that all the n numbers are smaller than 0.5, indicating a Fickian diffusion type of release for all the three cases. k is lower for release under 0.127 mL/min than that under higher flow rate of 1 mL/min, suggesting a faster release rate under higher flow rate. This is explained by that the higher concentration gradient under higher flow rate facilitates the higher release rate for a diffusion-dominated release. However, the k factor under static condition is even higher than that under flow conditions. To explain this phenomenon, we further introduce new release medium at the rate of 0.127 mL/min to LPG1 which is previously under static release condition, and find out that the release is actually not completed and LPG1 continues to respond to the new release medium. Figure 5 shows the response of the LPG1 when subject to new release medium at a flow rate of 0.127 mL/min. There is a blue shift, indicating a further drug release in LPG1. It is explained by the fact that under static condition, there may not be enough concentration gradient after the initial burst release since the total volume in the capillary tube is very limited (~84 μL), leading to the stop of the release process if there is no fresh release buffer introduced. This experiment shows that the commonly used method to obtain the release profile under static condition may not be accurate enough to predict the actually release of GS in vivo where a rich amount of interstitial flow exists. It is suggested that the profiles be obtained under a fluidic condition to better mimic the in vivo conditions to obtain more accurate release profiles.

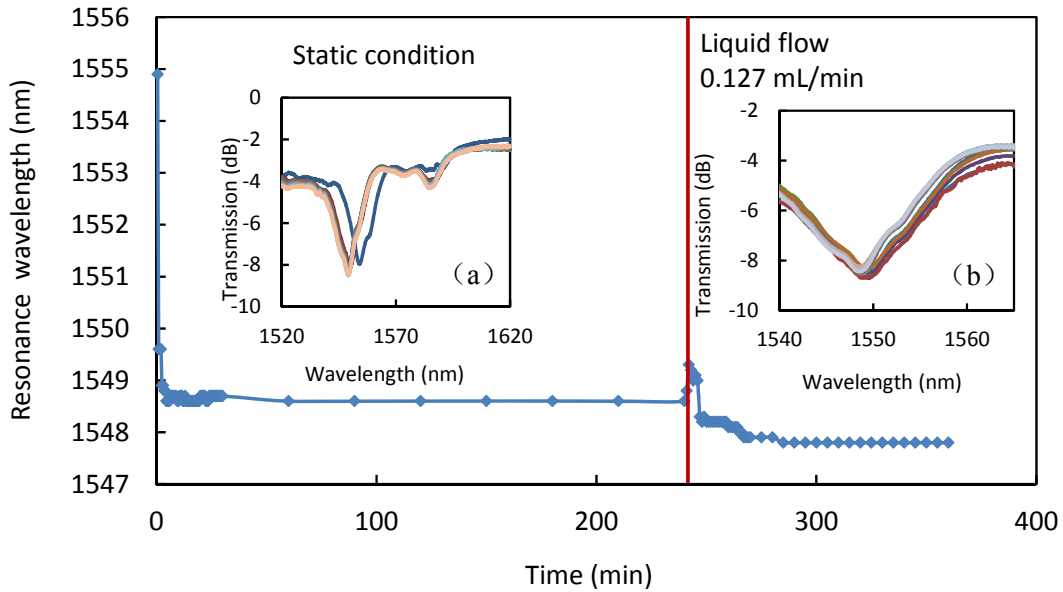


Figure 5. Response of LPG1 to the new releasing medium introduced at 0.127 mL/min. Insets (a) and (b) are the transmission spectra of LPG1 under static condition (the same as inset (a) in Figure 4) and the subsequent flow condition, respectively.

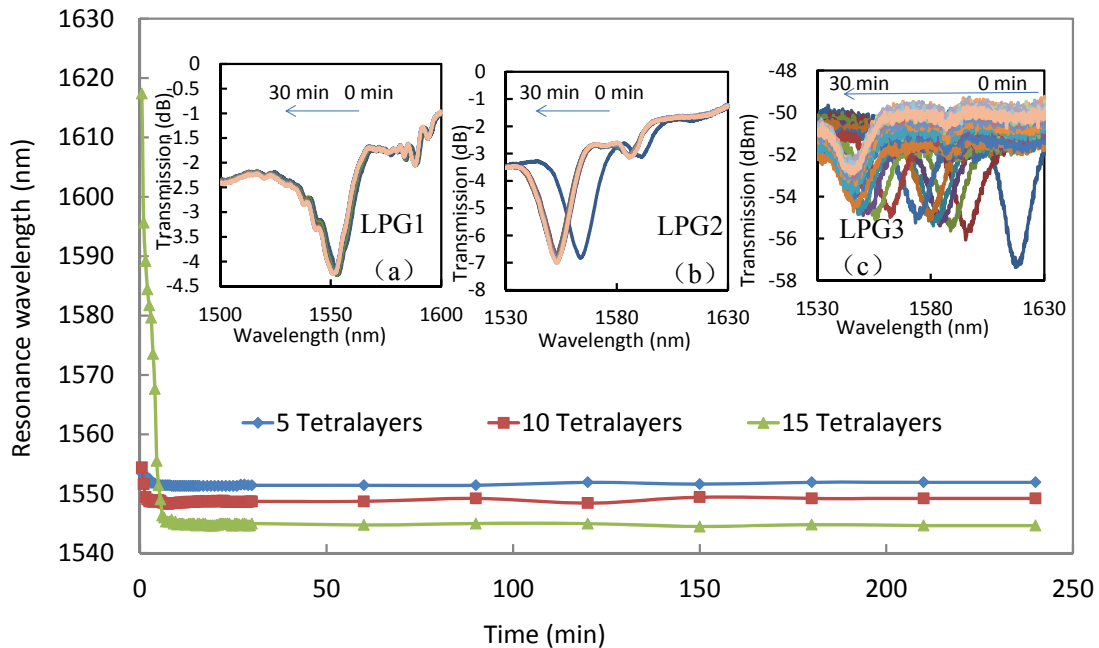


Figure 6. Responses of LPG1, LPG2 and LPG3 to the release of GS, respectively. Insets (a), (b) and (c) are the transmission spectra of LPG1, LPG2 and LPG3 with 5, 10 and 15 tetralayers under 0.127 mL/min flow condition recorded at 1 min time interval, respectively.

The influence of layer number of the tetralayer coating has also been evaluated. Three SMF-LPGs, namely LPG1, LPG2 and LPG3, with tetralayer number of 5, 10 and 15 are fabricated, respectively. The three SMF-LPGs with the coatings

are used to measure the drug release profiles of GS under the flow condition of 0.127 mL/min. Figure 6 shows the response of LPG1, LPG2 and LPG3 to the release of GS with tetralayer number of 5, 10 and 15, respectively. Table 3 summarizes the fitting parameters of the release profiles of LPG1, LPG2 and LPG3 using Peppas model, respectively.

Table 3. Fitting parameters for GS release of LPG1, LPG2 and LPG3 with tetralayer number of 5, 10 and 15 under flow rate of 0.127 mL/min.

Layer number	5 (LPG1)	10(LPG2)	15(LPG3)
	$y = 37 \cdot t^{0.32}$	$y = 34 \cdot t^{0.29}$	$y = 32 \cdot t^{0.37}$
k	37	34	32
n	0.32	0.29	0.37

Table 3 shows that the release rate is decreasing with the increase of the tetralayer numbers. It is true that the increase of the layer number results in a thicker coating, leading to a longer time for the GS to diffuse out of the polymer matrix, thus a slower release rate.

4. CONCLUSIONS

Our study shows that LbL assembly of drug-eluting polyelectrolyte thin films can be effectively carried out on and monitored by SMF-LPG. SMF-LPG capillary microfluidic system enables a powerful lab-on-fiber optofluidic platform for real-time and in-situ monitoring of drug release of the drug-eluting thin films. Release profiles depend on the liquid flow as well as the thickness of the drug delivery thin films. Higher flow rate results in a faster release rate, due to a higher concentration gradient. Whereas thicker tetralayer results in a slower release rate due to the thicker coating, thus a longer time for the drug to diffuse out for a diffusion-dominated release. Particularly, attention should be paid to the release profiles measured under static condition, since the drug release process may be stopped due to a lack of concentration gradient when there is no flow. It is suggested that release profiles be measured under physiologically relevant flow condition. SMF-LPG has proven a powerful lab-on-fiber optofluidic platform for the monitoring of the individual LbL steps both constructively and destructively. It forms the basis for SMF-LPG based lab-on-fiber optofluidic system as a powerful physiologically relevant test-bed for LbL drug release studies.

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