Biomimetic Nanocoatings as Novel Drug Delivery Systems

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Abstract: Orthopaedic implant-associated infection is one of the most common and problematic complications for patients having an orthopaedic procedure. In this study, our goal was to develop drug-eluting nanocoatings on orthopaedic implants to potentially prevent implant-associated infection. A novel nanotechnology, i.e., layer-by-layer self-assembly (LBL), was used to construct biocompatible polymeric nanocoatings. The load and release of various drugs including antibiotics were studied and controlled release of drugs was achieved.

Methods: Polymers, poly (L-lysine) (PLL) and poly (L-glutamic acid) (PLGA), and drugs (cefazolin, gentamycin, tobramicin, and methylene blue) were dissolved in phosphate buffer. Quartz slices, stainless steel and titanium plates were used as substrates. They were cleaned in piranha solution for 2h, washed in deionized water, and followed by rinsing with ethanol solution and deionized water, respectively. A schematic diagram for the LBL process and drug loading is shown in Fig. 1. The LBL process is as follows: (i) immerse a substrate in a polycation solution (i.e. PLL), for 15 min, rinse it for 2 min in phosphate buffer solution and dry it with air or N_2 gas; (ii) immerse the substrate in a polyanion solution (i.e. PLGA) for 15 min, rinse it for 2 min in phosphate buffer and dry it with air or N_2 gas; and (iii) repeat steps (i) and (ii) as necessary to obtain the desired number of layers. Drugs with different charge properties, i.e. positively-charged or negatively-charged, were loaded in the PLL/PLGA nanocoatings by incubating the nanotechnology coated substrates in a drug solution.

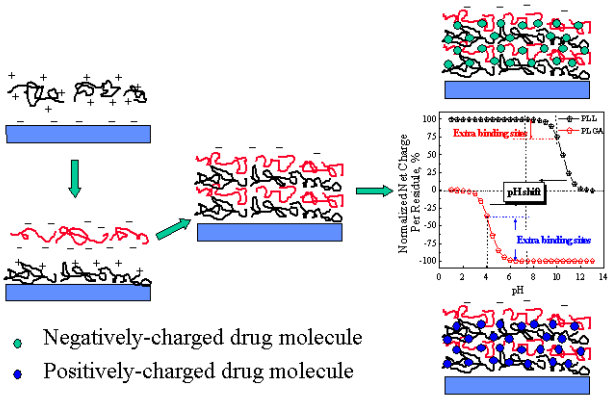

Fig. 1. A schematic diagram for the LBL process and drug loading.

Results & Discussion: PLL and PLGA are two important biodegradable biopolymers that have been studied extensively for a wide variety of surgical and pharmaceutical applications. PLL is positively-charged while PLGA is negatively-charged at neutral pH. PLL/PLGA nanocoatings were deposited on quartz slides, stainless steel and titanium plates using LBL. Three pH values were studied: pHs 4.0, 7.4, and 10.0. The formation of PLL/PLGA multilayer nanocoatings was monitored using UV-vis or Fourier transform infrared (FTIR) spectrometry (Fig.2a). The absorbance (i.e. the mass) of the PLL/PLGA nanocoatings on a quartz slide, an implant model, increased with the number of deposition layers. Also, the assembly behavior varied with the pH values of the PLL and PLGA solutions (data not shown).

FTIR spectroscopy confirmed the incorporation of antibiotics (e.g. cefazolin) in the nanocoatings on stainless steel and titanium plates (Fig. 2a, inset). The peaks at 1760 cm^{-1}, corresponding to cefazolin lactam vibrate (C=O), appeared after loading of cefazolin for 5 minutes.

The release behavior of incorporated drugs in the nanocoatings was investigated. A continuous release of drugs from the polypeptide nanocoatings was observed. The release of drugs can be controlled by number of layers (Fig. 2b), pH value of the releasing media, and cross-linking treatment of the nanocoatings.

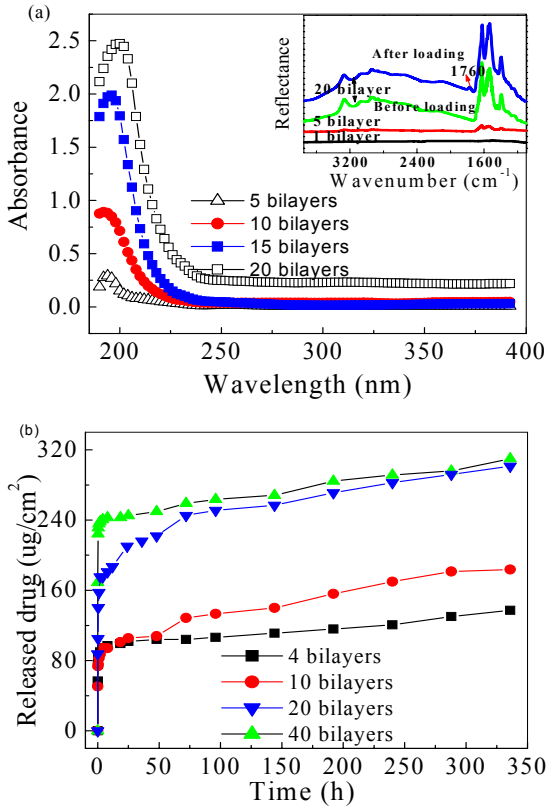

Fig.2. (a) Monitoring the formation of PLL/PLGA nanocoatings by UV-vis and FTIR spectrometry. (b) The release behavior of cefazolin from the nanocoatings on quartz slides. More cefazolin was released from samples with more layers.

Conclusions: Polypeptide nanocoatings can be deposited on orthopaedic implants such as stainless steel plates based on an advanced nanotechnology, and drugs including antibiotics can be loaded into the nanocoatings. The release of incorporated drugs can be controlled. The approach investigated could lead to the development of a novel strategy for local drug delivery for preventing implant-associated infection. Further *in vitro* and *in vivo* studies are under investigation.

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