Drug Elution Using Therapeutic Self-Assembled Monolayers

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Introduction: Though the bare metal coronary artery stents have reduced the angiographic restenosis rates up to 20-30 % [1], the occurrence of in-stent restenosis remains a significant problem. The biology of in-stent restenosis mainly includes thrombus formation and neointimal cell proliferation. Implantation of drug eluting stents (DES), in which the polymers are solely used as drug carriers, dramatically reduces the restenosis rates to 13 % [2]. However, the long-term clinical follow up of DES shows hypersensitivity and extensive inflammatory reactions to polymer coatings in some cases [3,4]. Hence, there is a need to develop an alternate stent based drug delivery systems that can release drugs in a controlled fashion without eliciting an adverse response. In this work, the therapeutics have been attached directly to the metal surface through self-assembled monolayers (SAMs) and the drug release kinetics from these therapeutic SAMs (T-SAMs) were evaluated.

Methods: Hydroxyl-terminated (-OH) SAMs were formed by immersing sputter coated gold substrates in 2mM solutions of 11-mercapto-1-undecanol in absolute ethanol for 48 hours. Aspirin, used as a model drug, was attached to the SAMs. 0.25 grams of aspirin was refluxed in 4 ml of thionyl chloride for 1 hour under nitrogen atmosphere. After roto-evaporating the excess thionyl chloride, 20 ml of dry-tetrahydrofuran (THF) was used to dissolve the acid chloride. Hydroxyl-terminated SAMs formed on gold substrates were then immersed into the acid chloride solution. One fifth of one milliliter of pyridine was added, and the mixture was kept under nitrogen for one hour. The samples were then rinsed with THF for 3 minutes and blown dried with nitrogen. Gold samples with aspirin functionalized SAMs (hereafter T-SAMs$_{(Aspirin)}$) were submerged in 7 ml of phosphate buffered saline solution (PBS) at 37 °C. A PBS aliquot was taken at 1, 3, 7, 10, 21 and 30 days and analyzed for the quantity of drug eluted. The gold samples with SAMs, T-SAMs$_{(Aspirin)}$, and post drug elution were characterized by X-ray photoelectron spectroscopy (XPS) and the PBS aliquots were characterized by high performance liquid chromatography (HPLC).

Results / Discussion: The higher binding energy (BE) in the C 1s spectrum of T-SAMs$_{(Aspirin)}$ specimens at 286.1 eV and 288.6 eV is assigned to the newly formed ether (C-O-C) and ester (O=C-O) bonds after the attachment of aspirin (Fig. 1). Also, the formation of the ester bond between the SAMs and aspirin is further supported by the higher BE peaks in the O 1s spectrum; the peaks at 531.7 eV and 533.1 eV are assigned to carbonyl oxygen and ester bonds respectively (Fig. 2). The HPLC characterization data of the PBS aliquots for the eluted aspirin is presented in Fig. 3. The hydrolysis of ester bonds between the SAMs and aspirin (drug-elution mechanism) is supported by the XPS studies on the ester components of C 1s and O 1s spectra in the drug eluted gold substrates.

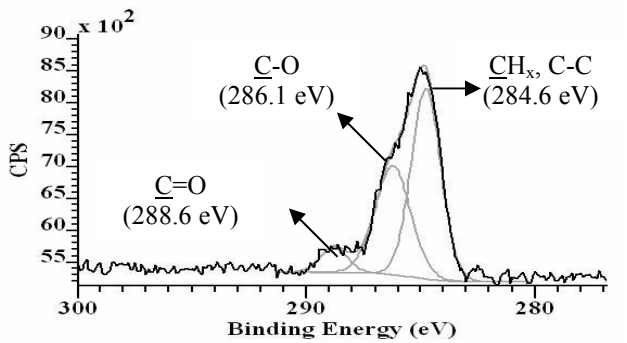

Figure 1. High-resolution XPS spectra of C 1s region for the T-SAMs$_{(Aspirin)}$ on gold substrates

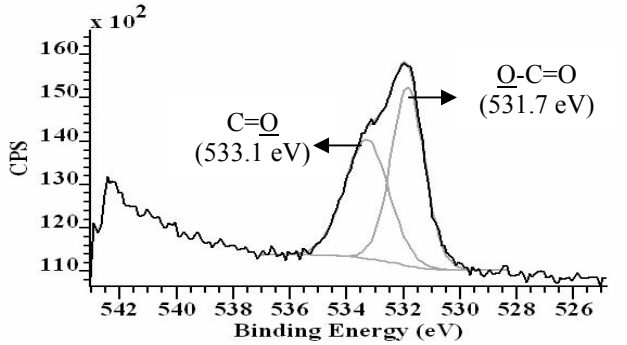

Figure 2. High-resolution XPS spectra of O 1s region for the T-SAMs$_{(Aspirin)}$ on gold substrates

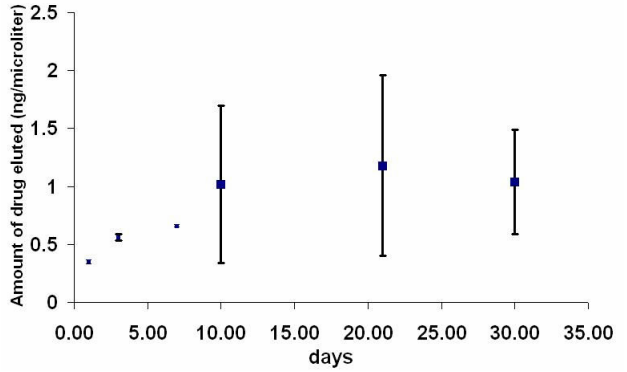

Figure 3.Cumulative *in vitro* drug release profiles for T-SAMs$_{(Aspirin)}$ on gold substrates

Conclusions: The proof of the concept of attaching therapeutics to the SAMs and releasing it from the T-SAMs is demonstrated by the XPS and HPLC techniques. T-SAMs have potential biomedical applications as an alternate approach for controlled drug delivery systems from metal implants.

References:

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