Effect of Processing Methods on Drug Release Profiles of Anti-restenotic Self-Assembled Monolayers

Susan E. Stoebner, Gopinath Mani

Biomedical Engineering Program, The University of South Dakota, Sioux Falls, SD 57107

Statement of Purpose: Polymer coatings in drug-eluting stents cause inflammatory and hypersensitive reactions in patients [1]. Hence, the use of self-assembled monolayers (SAMs) as a polymer-free drug delivery platform has been previously demonstrated [2]. Recently, an anti-restenotic drug, paclitaxel (PAT), was sustained released from an ultra-thin stent strut material, cobalt-chromium (Co-Cr) alloy, using SAMs. A microdrop deposition method [3] was used to load clinically relevant amount of PAT (100 µg/cm^2) on SAMs coated Co-Cr surfaces. A heat treatment after PAT deposition [3] was used as a processing method to obtain sustained release profiles of anti-restenotic SAMs (PAT deposited SAMs are referred to here as anti-restenotic SAMs – ASAMs). In this study, the effect of different processing methods such as room temperature treatment (RT), heat treatment (HT), cold treatment (CT), and quenching on the drug release profiles of ASAMs was investigated.

Methods: Carboxylic acid terminated phosphonic acid SAMs were coated on Co-Cr alloy samples (1cm × 1cm). PAT solution was prepared in ethanol at a concentration of 4 mg/mL. A 25 µL aliquot of the prepared PAT solution was placed on SAMs coated Co-Cr surfaces. The ethanol was allowed to evaporate for 3 hrs leaving behind a thin PAT film (100 µg/cm^2) on SAMs coated surfaces. Thus prepared PAT deposited specimens were processed under the following four methods: (a) RT – specimens were treated at 20 °C for 3 hrs; (b) HT – specimens were heat treated at 70 °C, 100 °C, and 140 °C for 3 hrs; (c) cold treatment – specimens were cold treated at -20 °C for 3 hrs; (d) quenching – specimens were heat treated at 140 °C for 3 hrs followed by immediate immersion in water for 1 hr. All PAT coated specimens processed by the above described methods (n = 4 each) were immersed in phosphate-buffered saline/Tween-20 (PBS/T-20) at 37 °C for up to 28 days. PBS/T-20 samples were collected at 1, 3, 5, 7, 14, 21, and 28 days and were analyzed for the amount of drug released using high performance liquid chromatography. PAT deposited specimens were characterized using scanning electron microscopy (SEM), atomic force microscopy (AFM), and Fourier transform infrared spectroscopy (FTIR) for studying the morphology, distribution, and solid-state of PAT on SAMs coated Co-Cr under different processing conditions.

Results: *In vitro* drug release profiles of RT and HT specimens showed sustained release of PAT for up to 28 days (Fig 1). The CT and quenching specimens showed biphasic drug release profiles – an initial burst release in days-1 to 3 was followed by a sustained and slow release for up to 28 days. SEM images showed spherical and ovoid shaped morphologies of PAT on RT (2 – 8 µm in size), HT (1 – 4 µm), and CT (1 – 4 µm) specimens while needle shaped PAT crystals were observed on quenched specimens (Fig 2). AFM images showed the growth of PAT crystals on alloy surfaces in concentric circles (Fig 3). In FTIR, the presence of a singlet or doublet carbonyl peak at 1720 cm^{-1} is commonly used to determine the solid-state of PAT. RT and HT showed a doublet carbonyl peak (dihydrate crystals) while CT and quenching showed a singlet carbonyl peak (amorphous form).

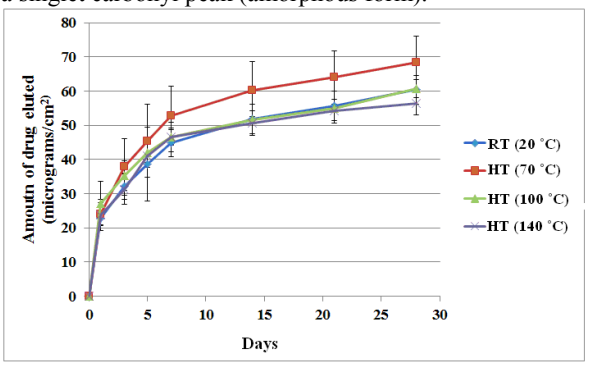

Fig 1. *In vitro* PAT release profiles of RT and HT.

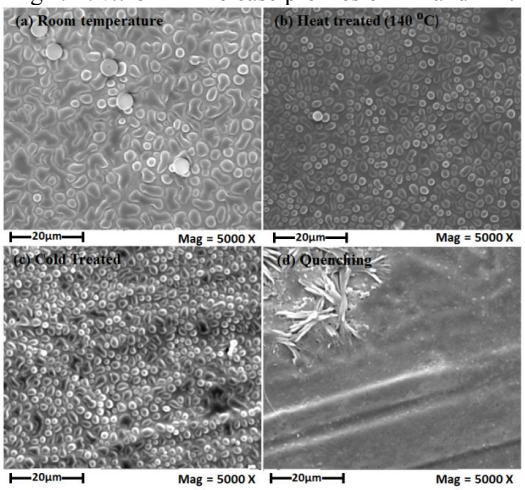

Fig 2. SEM images of RT, HT, CT and quenching.

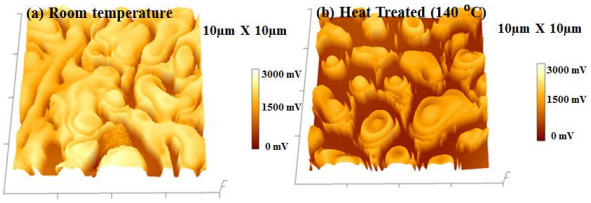

Fig 3. AFM tapping mode 3D phase demodulation images of (a) RT and (b) HT specimens.

Conclusions: This study demonstrated that processing methods have significant impact on the morphology, distribution, and solid-state of PAT on SAMs coated Co-Cr. These factors altogether decide the type of drug-release profiles of anti-restenotic SAMs.

References: (1) Mani G *et al*. Biomaterials 2007, 28, 1689 (2) Mani G *et al*. Biomaterials 2008, 29, 4561 (3) Mani G *et al*. Biomaterials 2010, 31, 5372

Acknowledgements: This study was supported by a National Scientist Development Grant Award (10SDG2630103) from the American Heart Association.