A Comprehensive Approach for Real-time Drug Release Imaging from Polymeric Coatings

John Foley¹, Robert Hoerr¹, Mike Matuszewski¹, Judit Puskas², Greg Haugstad³, Jinping Dong³, Chris Frethem³

¹Nanocopoeia, Inc, St. Paul, MN, ²University of Akron, Akron, OH, ³University of Minnesota Characterization Facility, Minneapolis, MN.

Statement of Purpose: Drug release from polymeric compounds is a highly complex and poorly understood process. Release from samples is usually non-linear and the mechanisms that control release are not known. The traditional approach of measuring percent release over time provides researchers with only a grainy snapshot of the process. The purpose of this study was to take a comprehensive approach to examine drug sequestration, mobilization and release from a polymer immersed in PBS to better understand how to engineer coatings to tailor release profiles to meet biological objectives.

Methods: An arborescent polyisobutylene-polystyrene (arbIBS) block copolymer was created by living carbocationic polymerization¹. Coatings were applied to 0.2”x0.4” stainless steel coupons by ElectroNanospray (Nanocopoeia, Inc., St. Paul, MN) of a 1%/0.1% polymer/drug solution. The final coating contained 10 wt% drug (rapamycin) in a arbIBS polymer matrix. High pressure liquid chromatography (HPLC) analysis of rapamycin release was performed on a Hewlett Packard 1090 HPLC system. SEM analysis of uncoated samples was carried out at 1.0 kV accelerating voltage using a Cold Field Emission Gun Scanning Electron Microscope (Hitachi S-4700; Pleasanton, CA). 4D confocal Raman spectroscopy was carried out with a Witec confocal Raman microscope (Ulm, Germany) fitted with an Omniclone Argon ion laser with 514.5nm excitation and 50mW maximum output power. Atomic force microscopy was carried out using a Molecular Imaging PicoPlus/PicoScan 3000 system (now Agilent 5500; Santa Clara, CA) with environmental control (RH, T) and liquid cell, and the Witec Digital Pulsed Force Mode attachment to obtain images of height, tip-sample adhesion, stiffness and viscoelastic character.

Results: arbIBS/rapamycin films were sprayed onto stainless steel coupons; coating morphology was found to be a smooth, closed matrix by SEM. Identical samples were incubated in phosphate-buffered saline and drug release measured by HPLC. Post-release films were dried and uncoated samples were examined by SEM. The morphology contained evenly distributed micron-scale (~2-3 µm) pits which contained smaller, ~100 nm scale pitting. Identical samples were next examined by 4D confocal Raman microscopy. 4D Raman imaging revealed that the drug segregates into discrete micron sized columns that can span the bulk of the polymer depthwise. These columns are similar in size and distribution to the surface pitting that was observed by SEM. The drug was found to rapidly mobilize (< 5 min.) after immersion in PBS. Imaging captured over the 12 hour release period showed that the drug diffuses out of the concentrated columns and migrates upward towards the surface of the polymer. Raman images are diffraction limited and thus, the complementary approach of AFM was used to examine drug distribution at nanoscale level. AFM data obtained before immersion showed discrete, 80 – 120 nm domains of decreased adhesion suggesting that the drug is sequestered in nanoscale domains throughout the polymer as well as in clusters within the larger microscale domains. In-liquid AFM after 18 hours showed discrete holes of similar dimensions.

Conclusions: In order to better engineer drug eluting materials it is essential to understand how the drug and polymers behave in aqueous environments. SEM, 4D confocal Raman microscopy and in-liquid AFM are powerful, complementary tools that can help to deepen our understanding of this important process.

References: