Quantitative Assessment of Drug and Polymer Distribution in the NEVO™ Sirolimus-eluting Coronary Stent Reservoirs from Explanted Porcine Samples over Time by Vibrational Spectroscopy

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Statement of Purpose: Minimizing vessel-polymer interface and avoiding durable polymer implantation may enhance long term safety of drug-eluting coronary stents. In contrast to conformal-coated stents, the NEVO™ Sirolimus-eluting Coronary Stent (Cordis Corporation, Bridgewater, NJ) is designed with a unique RES TECHNOLOGY™, which incorporates hundreds of small reservoirs, each acting as a depot for drug delivery. The stent is made of cobalt chromium, which makes it flexible and conformable with thin struts to maximize vessel coverage. The formulation within each reservoir contains a biodegradable polymer matrix composed of poly (D,L-lactic-*co*-glycolic acid) [PLGA] with the proven therapeutic agent sirolimus. PLGA is an established biomaterial that breaks down into glycolic and lactic acid that is secreted by the body. We are developing methodologies that can chemically image both the drug and polymer spatial distributions within the reservoirs from explanted stents from porcine models. Specifically, confocal Raman microscopy (CRM) and Fourier Transform Infrared (FTIR) microscopy combined with multivariate data analysis is used to generate quantitative calibration curves for sirolimus, PLGA content, and the monomer ratio of PLGA. These calibration curves can then be used to visualize the drug release and polymer erosion as a function of time. We are interested in using this information in establishing the precise time for drug release and complete polymer degradation in vivo.

Methods: As shown in Table 1, a series of formulation standards were prepared on NEVO™ stents that varied in the type of PLGA and the concentration of sirolimus.

Table 1. Formulation Standards

PLGA type	wt% Drug
75:25	0%
75:25	35%
75:25	50%
75:25	65%
65:35	0%
65:35	35%
65:35	50%
65:35	65%
85:15	0%
85:15	35%
85:15	50%
85:15	65%

A confocal Raman microscope equipped with both 532 and 785 nm excitation wavelengths was employed to collect nondestructive cross-sectional spectral depth profiles through the reservoir inlay. The spatial area mapped is approximately 800 μm^2/reservoir. A typical FTIR microscope spatial profile mapped is approximately 15000 μm^2 /reservoir with 4 cm^{-1} resolution and 128 scans. Average spatial area partial least squares (PLS) regression models are generated first to compare to analytical assay values. The quantitative models are tested on independent sample sets to gauge the accuracy and precision of the predictions. Quantitative spatial models are then generated by partial least squares (PLS) analysis after spectral image preprocessing is performed to visualize distribution of components.

Results: Three separate PLS models for sirolimus, PLGA content, and PLGA monomer ratio were developed for confocal Raman microscopy measurements and the models were validated on a test lot. Similarly, three separate PLS models were developed for FTIR microscopy measurements and the models validated on a test lot. Excellent agreement was observed between the predicted values and the analytical assay values for the test lot. The average spatial area models are useful to benchmark the methods against an analytical assay method and give a level of confidence for the image models. Quantitative bitmap image methods were then developed. An example polymer distribution image is shown in Figure 1. We used this same methodology to image explanted stents from porcine models at 30, 60, 90, and 120 days. The drug distribution within the polymer was characterized as a function of implant time. The majority of drug is released by day 60. The majority of polymer is removed from the reservoir by day 90.

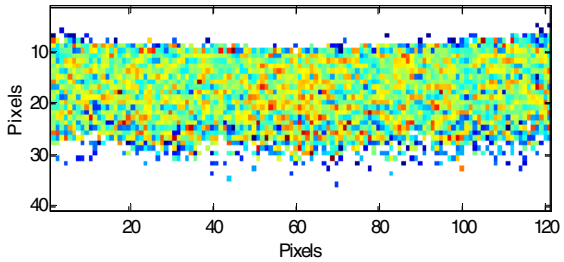

Figure 1. Polymer distribution image of a reservoir in a NEVO™ development stent.

Conclusions: Using appropriate formulation standards, quantitative models were built to describe the sirolimus and polymer found in the NEVO™ Stent. Using both CRM and FTIR microscopy, explanted stents were analyzed to visualize the drug and polymer distribution as a function of time. Results showed that the majority of drug is released by day 60 and the majority of polymer is removed from the reservoir by day 90. Neither drug nor PLGA was observed at day 120.