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Biomaterial Considerations for Drug-Eluting Stents

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Abstract— The ultimate test for implant biomaterials is determined by the long-term, post-market clinical product performance. This is a key consideration in the initial design and development for drug-eluting stents. To insure this ultimate clinical success, a rigorous series of bench-top, preclinical and clinical evaluations must be performed. The factors in the biomaterial choice which are important for each stage in this development process include pharmaceutical, physical, and biological elements. This presentation will outline the steps taken by Boston Scientific in each of these stages to achieve the desired clinical end-points.

I. INTRODUCTION

CARDIOVASCULAR implants require a unique set of biomaterial performance requirements. In general, the biological response to an implanted stent should be pro-healing with regard to endothelium regeneration in combination with being both anti-inflammatory and anti-thrombotic.

The development and commercialization of drug eluting stents as cardiovascular implants has resulted in dramatic improvements in the clinical success rate for coronary interventions [1]. In addition, both the device design constraints and pathology of coronary restenosis impose some unique requirements in the development of controlled release technology for these applications [2]. For example, the deliverability requirements for the stent severely limit the amount of surface area and coating thickness that can be utilized for drug delivery. Furthermore, in response to the acute injury of percutaneous transluminal coronary angioplasty (PTCA), the drug should be released promptly to the lesion site post implantation. On the other hand, coronary restenosis is a non-acute phenomenon, thus also requiring a long-term, sustained controlled release of the active pharmaceutical agent over several months [3].

The combination of these controlled release needs with mechanical and biological requirements that can be severe in cardiovascular application make biomaterial selection a key component of the success of drug-eluting stent design.

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A. Bench-top Testing

Bench-top testing is important throughout the development process of drug-eluting stents. This includes preformulation and formulation work that involves characterization of drug to polymer interactions, drug release profiles, polymer and drug polymorphism, as well as mechanical considerations such as coating adhesion and particulation.

Evaluation of mechanical integrity of the stent and stent coating are integrally related to the properties of the biomaterials used as excipients and carriers. Biomaterials used for stent coatings must withstand the stresses of stent expansion, tracking through potentially tortuous vessels and calcified lesions. Stents and stent coatings designed for cardiovascular application also have significant challenges with regard to chronic mechanical integrity.

Furthermore, combination devices require control of drug stability and elution control, and degradable systems require understanding of the degradation pathway including particulation and bioabsorption. Bench-top testing for the above design elements is a key component in early stage product development for evaluating biomaterial selection for drug eluting stents as well as for qualification of these products.

For biodegradable systems, in addition to the above tests, a number of additional considerations must be studied. These include the rate and pathway of degradation, biological effects of the degradation byproducts, and potential of these byproducts to interact with the drug.

B. Preclinical Evaluations

For pre-clinical evaluations of vascular implants, a variety of animal models may be employed, including porcine, rabbits and rats/mice. Historically, pigs have been the preferred animal model for evaluation of vascular performance. [4]

The normal process of stent healing initially involves the deposition of plasma protein and/or a thrombotic coating of fibrin adherent to or associated with struts and containing variable amounts of red blood cells (RBCs), platelets, and leukocytes. [5] The biomaterial used for the stent, and drug coating in drug-eluting stents, provide the substrate for this initial biological interaction with the stent implant.

Short and long term outputs of preclinical studies include evaluations of efficacy, histological safety, and device mechanical stability. For combination devices this can also include pharmacokinetic and pharmacodynamic evaluations.

C. Drug-eluting stent Coating Characterization

Once biomaterials are selected for development for stent and stent coating, a battery of characterization tests are used to fully characterize the performance of the final product in addition to the bench-top and preclinical studies mentioned above.

These systems often require in-depth physical characterization studies to understand the detailed product performance attributes. These may include, for example, surface characterization techniques such as AFM, TOF-SIMS, XPS, SEM and confocal Raman, to name a few.

An example of this is shown in Figure 1, which is an AFM image of the surface of a TAXUS™ Express stent. The microstructure of the drug coating for this system is revealed to be a phase separated system where paclitaxel, in particulate form, is uniformly suspended and distributed throughout the polymer coating. After stent implantation, the drug that has access to the surface is released from the stent and diffuses into the vessel wall.

The outputs of these studies are then combined with computational models to provide an in-depth understanding of the final product. [3]

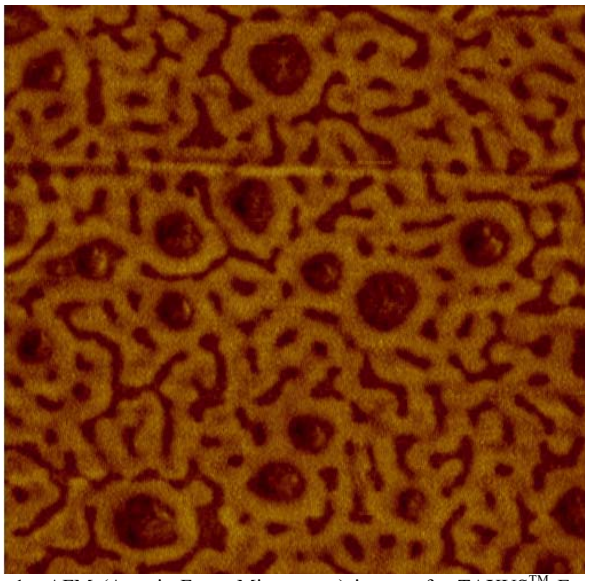

Fig. 1. AFM (Atomic Force Microscopy) image of a TAXUS™ Express Stent showing the surface of paclitaxel particulate surrounded by polymer matrix

II. Conclusion

Bench-top testing, preclinical studies, and detailed physical characterization of coatings have been summarized that aid in biomaterial selection for drug-eluting stent development. These same principles are applicable to other devices where combinations of pharmaceutical product performance interact in complex ways with mechanical stresses and biological phenomena in areas such as oncology, urology, heart valves, ocular implants, and leads for cardiac rhythm management.

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