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Research Paper

Degradation and adhesive/cohesive strengths of a reservoir-based drug eluting stent

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ABSTRACT

This paper presents the results of loss of mechanical strengths due to the degradation that occurs in a model reservoir-based coronary stent, the NEVO™ Sirolimus-eluting Stent (NEVO™ SES). The adhesion of the formulation to the reservoir and cohesion within the formulation in the time course of hydrolysis were determined using a micro-testing system that was developed specifically for the measurements of the adhesive and cohesive strengths of suspended polymeric films. The strengths were measured after hydration, during degradation with gentle agitation, as well as degradation with pulsatile mechanical loading. The morphology and molecular weight changes in the time course of NEVO™ SES formulation degradation were also studied using Scanning Electron Microscopy (SEM) and Gel Permeation Chromatography (GPC) techniques. Morphological changes, such as pore formation, lagged behind the decrease in the molecular weight of the formulation. In contrast, the adhesion/cohesion strengths showed that the mechanical integrity of the stents dropped significantly within a few hours of hydration, before reaching a plateau. Despite the significant molecular weight decrease and morphological changes, the plateau mechanical strengths reached were essentially the same during degradation, under both, mechanically unloaded and loaded conditions.

1. Introduction

Drug-eluting stents (DES) have demonstrated efficacy in the treatment of coronary artery disease in combating the re-narrowing of the stented artery, known as restenosis (Fattori and Piva, 2003; Price et al., 2009; Li et al., 2011). The first generation DES are typically composed of metallic scaffolds, conformally coated with a mixture of cytotoxic or cytostatic drugs and durable polymers. The adhesion of the coatings on DES systems have also been studied using microscopy (Strickler et al., 2010), nano-scratch techniques (Tang et al.), nano-indentation methods (Burke et al., 2008), atomic force microscopy (AFM) (Wolf et al., 2008). These studies have shown that the surface energy of the coatings to the usually metallic substrate (~0.2 Jm^{-2}) is on the same order as the cohesive surface energy of plastics (Burke et al., 2008; Wolf et al., 2008). This explains why these coatings do not delaminate from their substrates after manufacturing. All the

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prior work has been done with stents fresh-out-of-package that have not been subjected to simulated use environment.

However, recent concerns about the long-term safety of lifetime implants have emerged (Li et al., 2011). Several years after implantation, a small number of patients have developed long-term thrombosis, which is thought to be due to the residual effects of the durable coatings that were used in the first generation of the DES (Li et al., 2011). Hence, to avoid the use of durable coatings, degradable systems have been studied recently (Price et al., 2009; Colombo and Karvouni, 2000; Soares et al., 2010), either as coatings (Price et al., 2009), or as entire stents (Colombo and Karvouni, 2000; Soares et al., 2010). One common family of degradable polymers for stents is (poly-lactide-co-glycolide) (PLGA) (Colombo and Karvouni, 2000; Soares et al., 2010; Park, 1995).

PLGA polymers hydrolyze upon implantation to release carboxylate and alcohol containing oligomers and monomers. This hydrolysis generates polymer chains of lower molecular weight, which are initially trapped in the bulk of the implant. When very low molecular weight fragments are generated, they dissolve in water, forming pores in the bulk of the implant. Eventually, the entire implant dissolves, and the mechanism of degradation is described as bulk erosion (Park, 1995; Lu et al., 2000; Engineer et al., 2011). It has been demonstrated that PLGA systems degrade, generating water-soluble oligomers and monomers (Park, 1995; Lu et al., 2000; Engineer et al., 2011).

In the case of controlled release formulations containing PLGA polymers and drugs, several parameters influence the reaction described above, such as the dimensions and location of the implant. Hydrolysis can also occur, with or without the application of mechanical load, which may influence the degradation. For example, Fan et al. (2008) have shown that degradation in the presence of compressive and/or tensile load differs from degradation under unloaded conditions. In addition, medical devices are terminally sterilized commonly using e-beam or γ-sterilization. The interaction of a high-energy beam with the polymer leads to chain scission, further impacting the mechanism of hydrolysis.

One such prototype stent, the NEVO^{TM} Sirolimus-eluting Coronary Stent (NEVO^{TM} SES) (Fig. 1) by Cordis Corporation, a Johnson & Johnson company, comprises of an L605 Co-Cr alloy scaffold with hundreds of micron-scale reservoirs that contain a mixture of sirolimus and (poly-D, L-lactide-co-glycolide). Porcine safety studies have shown that the NEVO^{TM} SES formulation fully degraded in about 90 days (Price et al., 2009).

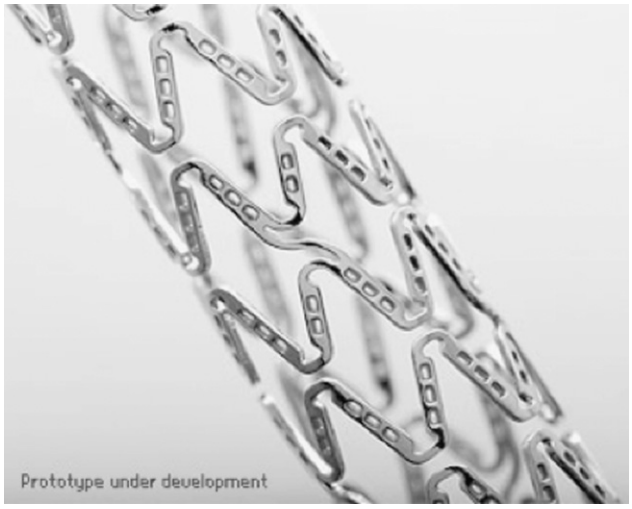

Fig. 1 – Optical microscopy image of NEVO^{TM} SES.

In an effort to evaluate the adhesion of the formulation to the surrounding reservoir, and the cohesion within the formulation inlay, a micron-scale push-out testing technique was developed (Shan et al., 2012). This was used to study the cohesive and adhesive strengths in freshly manufactured NEVO^{TM} SES. Prior work has shown that small probes induce cohesive failure, whereas larger probes induce adhesive failures (Shan et al., 2012).

This paper presents the results of the first ever study of adhesion and cohesion as a function of degradation for the NEVO^{TM} SES. Hydrolysis studies were performed without and with the application of cyclic load. The work focused on both, the failure between the metallic reservoir and the formulation, and the failure within the formulation. In addition to the adhesion/cohesion measurements, hydrolyzed samples were evaluated for their morphology and molecular weight during the time course of degradation of NEVO^{TM} SES. The results show a correlation between adhesion/cohesion strengths and degradation.

2. Material and methods

2.1. *Micro scale push-out tests on* NEVO^{TM} *SES*

The NEVO^{TM} SES samples (Fig. 1) that were used in this study were provided by Cordis Corporation, Spring House, PA. They were tested within 2–3 months of the date of manufacturing. The testing system and method have been described in detail in Shan et al. (2012). Essentially a tungsten probe was driven by a piezo-transducer to apply loads to the suspended formulation within the reservoirs of NEVO^{TM} SES (Fig. 2). Under *in situ* microscopic imaging, the critical load for failure was recorded. In the scope of the current work, both a small probe (10 μm × 20 μm × 50 μm, Fig. 3a) and a large probe (45 μm × 90 μm × 120 μm, Fig. 3b) were used. The suitability of the testing system was also verified daily using a standard

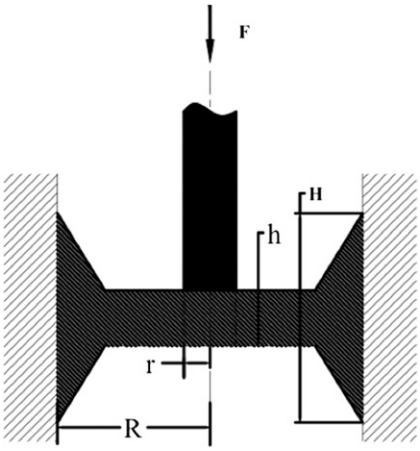

Fig. 2 – Simplification of NEVO^{TM} SES mechanical testing system.