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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).

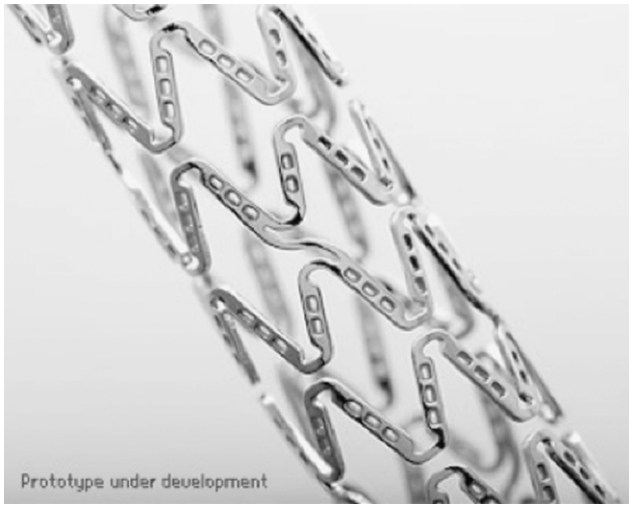

Fig. 1 – Optical microscopy image of NEVO^{TM} SES.

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

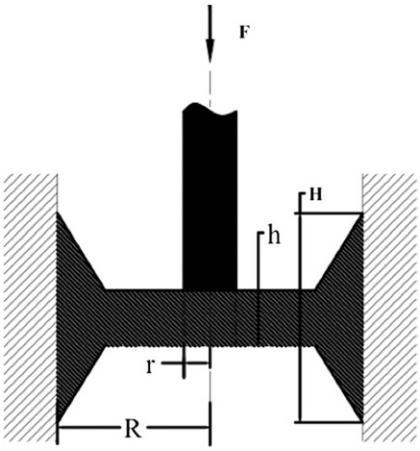

Fig. 2 – Simplification of NEVO^{TM} SES mechanical testing system.

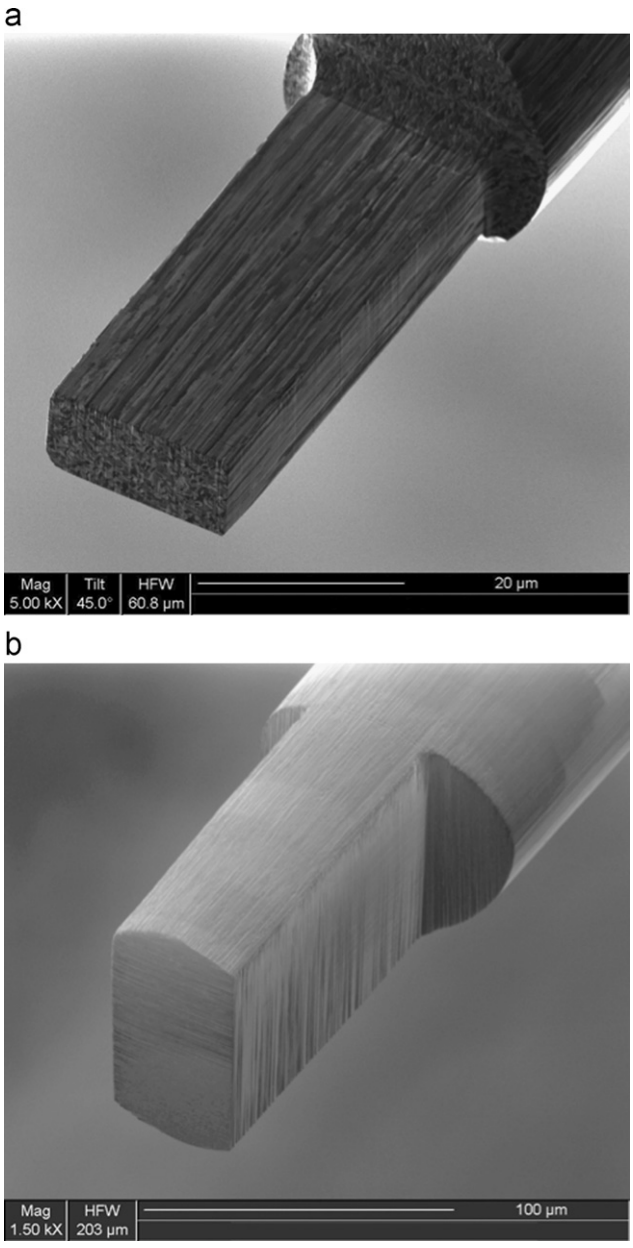

Fig. 3 – (a) Small tungsten probe with cross-section 10 μm × 20 μm; and (b) large tungsten probe with cross-section 45 μm × 90 μm.

polycarbonate thin film, prior to stent testing (Shan et al., 2012). Each set of tests, including the daily suitability check, was conducted five times.

2.2. *Sample preparation for hydrolyzed stents*

The stents were tested after various exposures to water, as follows:

(1) Exposure to high relative humidity: The stents were placed in a sealed chamber containing a saturated sodium chloride solution, which maintained 75% relative humidity. After 3, 24 and 72 hours of exposure, the stents were tested for adhesion/cohesion strengths with large and small probes.

(2) Short term hydrolysis: The stents were placed in deionized water for 1, 3, 12, 24 and 72 hours, respectively. The samples were then air-dried for 30 min before testing to determine the adhesion/cohesion strengths with large and small probes.

(3) Long term hydrolysis in test tubes: The stents were exposed to simulated physiological conditions that were based on the ASTM F1635-04a Code entitled, "Standard Test Method for In Vitro Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants." All the NEVO^{TM} SES were deployed into individual vials. Phosphate buffered saline (PBS) (pH 7.4, 4 mL) was added to each vial before conducting in vitro degradation studies under simulated physiological conditions in an orbital shaker maintained at 37 ± 2 °C with gentle agitation at 65 revolutions per minute (rpm).

At regular intervals, samples were removed for analysis. Sink conditions and adequate buffering capacity were maintained by removing the media and adding fresh PBS at weekly or biweekly time intervals. The samples were degraded for 1, 3, 8, 14, 30, 60 days, respectively. At each time point, the samples were removed from the media, rinsed with deionized water, dried with nitrogen, and stored at −20 °C. To measure adhesion/cohesion strengths, the samples were thawed to room temperature and tested.

(4) Long term hydrolysis in fatigue tester: To evaluate the degradation of the NEVO^{TM} SES under mechanically loaded conditions, a Cordis' Next Generation Coating Durability Tester (NGCDT) was used. This tester performed fatigue conditioning with the general test parameters identified in ASTM F2477-06 code entitled, "Standard Test Methods for in vitro Pulsatile Durability Testing of Vascular Stents." The testing conditions included the following conditions: (1) physiological pulse rate cycling at 1.2 Hz; (2) physiological temperature of 37 °C, (3) physiological pressure and HPLC grade water solution with biological growth inhibitors.

Water was utilized instead of phosphate-buffered saline to prevent corrosion of the metal fatigue equipment, which may interact with the NEVO^{TM} SES inlays. The tester fatigued 30 stent pairs at a time. To simulate a clinical environment, a pair of stent was deployed under simulated use conditions: each stent was tracked through a tortuous track that simulated aggressive coronary anatomy, and deployed in a silicone mock artery. A second stent was then deployed in the same manner with a ~5 mm overlap. Each stent was then over-expanded using a balloon catheter to the maximum allowed diameter for the design. After all mock artery modules were installed on the NGCDT, pulsatile loading at 1.2 Hz was initiated. Periodic distension and flow measurements were conducted to ensure the proper operation of the equipment. Stent pairs were degraded for 21, 42, 63, and 84 days, respectively. They were removed from the mock artery modules for analysis.

To preserve the hydrolyzed samples, after removal from the mock arteries, the stents were rinsed with deionized water, dried with a stream of nitrogen, and stored in the freezer at −20 °C. To measure adhesion/cohesion, the samples were thawed to room temperature and tested.

(5) Freeze–thaw cyclic thermal loading: The stents that went through one or more freeze-thaw cycles were tested

to evaluate the effect of sample storage on the mechanical properties of the formulation. The stents were first dipped into deionized water for 1 h, which was followed by one or more freeze–thaw cycles. One freeze–thaw cycle involved keeping the sample into a freezer at −20 °C for 24 h, and taking it out into lab air at 25 °C for 1 h of thawing. The stents were then tested for adhesion strength with a large probe.

2.3. Molecular weight changes during the lifetime of the NEVO™ SES

At each time point, three stents were recovered from the degradation media, gently washed with distilled water, dried under a flow of nitrogen and dissolved in tetrahydrofuran, THF (400 μ L). The solution was analyzed by Gel Permeation Chromatography (GPC). Molecular weights were calculated using polystyrene standards (Mw from 580 to 377,400, Polymer Labs).

2.4. Morphology changes during the lifetime of the NEVO™ SES

Scanning electron microscopy (SEM) was performed on a Zeiss EVO SEM (Carl Zeiss SMT Inc, USA) to characterize the appearance of the formulation inlays inside the reservoirs. Samples for hydrolysis in the fatigue tester at 21, 42, 63, 84, 98 and 126 days were evaluated, in order to capture the morphological changes in the time course of degradation.

3. Theory

3.1. Finite element modeling (FEM)

FEM was performed to study the effects of probe tip sizes on the failure modes. The Abaqus™ finite element software package (Dassault Systemes Simulia Corp., Providence, RI, USA) was used to compute the stress distributions associated with different probe tip sizes. An axisymmetric model was used as a simplification of the three-dimensional geometry (Shan et al., 2012).

In this model, the probe was approximated as a cylinder, while the reservoir was approximated as a hollow cylinder that contains the polymer film. The thicknesses of the surrounding metal and the geometry of the suspended film were based on simplified geometries of NEVO™ SES. The length of the probe tip was 80 μm. It was assumed that all the materials exhibited isotropic elastic behavior. The axisymmetric boundary condition was applied at the symmetry axis. Also, the outside edge of the stent was fixed to have no displacements and rotations. Vertical displacement was applied to the top of the probe. The adhesive interactions allowed no relative displacements between the probe and the formulation inlay at the contact interface (Shan et al., 2012).

Two simulations, one with a relatively small probe and one with a relatively large probe were performed. The principal stress distribution and the Von Mises stress distribution were both calculated. In both sets of stresses, the stresses are highest underneath the probe. However, when a large probe is used, the stresses near the interface of formulation inlay and the stent are also high. As the probe displacement increases, the stresses at the formulation inlay and stent interface increase, until they are sufficient to promote interfacial failure and inlay push-out. For the same displacement, the large probe applied larger force on the inlay than the small probe. Also, the stress concentrations beneath the probe decreased with the increasing probe tip size, while the stresses along the formulation inlay and stent interface increased. This suggests that the larger probe tip is more likely to promote adhesive failure along the formulation inlay and stent interface, than cohesive failure within the formulation inlay (Shan et al., 2012).

3.2. Theoretical modeling for failure modes transition in push-out test

Consider the general case of a force applied to a circular probe that was used to push against a suspended film, as shown in Fig. 2. In the case where interfacial stresses are sufficient to induce failure between the side walls and the polymeric film, the interfacial shear strength τ_i, is given by:

$$\tau_i = F_i/(2\pi RH) \quad (1)$$

where F_i is the force required to induce interfacial failure, R is the radius of the polymeric film and H is the depth of the interface (Fig. 2). Similarly, for smaller probe sizes, cohesive failure may occur when a cohesive circumferential crack is induced around the probe tip and pushed through the film thickness. Under such scenarios, a lower bound estimate of the cohesive strength is given by the condition in which the crack has propagated completely through the thickness. This gives:

$$\tau_c = F_c/(2\pi rh) \quad (2)$$

where F_c is the force required to induce cohesive failure occurs, r is the probe tip radius and h is the thickness of the film in the middle section. Since τ_i and τ_c may be considered as measurements of strength, then the transition from cohesive failure to adhesive failure may be determined from the critical condition at which the force required for interfacial failure F_i becomes equal to that required for cohesive failure F_c. From Eqs. (1) and (2), this critical condition, i.e. $F_i = F_c$, gives:

$$r_{trans} = RH\tau_i/(\tau_c h) \quad (3)$$

where r_{trans} denotes the probe size when the transition occurs. When $r < r_{trans}$, we have $F_c < F_i$ and the suspended film undergoes cohesive failure when the applied external force F reaches F_c first; when $r > r_{trans}$, we have $F_c > F_i$ and the suspended film undergoes adhesive failure when the applied external force F reaches F_i first. Hence, a transition should occur from cohesive failure at small probe tip radius to interfacial failure at larger probe tip radius, with a critical probe size r_{trans} given by Eq. (3), as shown schematically in Fig. 4. Thus, the cohesive strengths can be determined from the cohesive failures induced by a small probe, while adhesive strengths from adhesive failures induced by a large enough probe.

4. Results and discussion

4.1. *Exposure of* NEVO^{TM} *SES to high relative humidity*

The stents were exposed to 75% relatively humidity for 3, 24 and 72 hours, respectively. Water uptake was expected because PLGA is a hygroscopic polymer. However, since the exposure was brief, no hydrolysis was expected. Indeed, GPC analysis showed that the molecular weight of the polymeric formulation did not change during this brief exposure to moisture (Fig. 5). Also, SEM analysis indicated no detectable morphological changes, which were only observed after 21 days of degradation (Fig. 6).

In contrast, the critical forces for failure gradually decreased (Fig. 7). Specifically, when evaluating adhesion by a large probe, the forces to failure decreased from a level of 80 mN, for NEVO^{TM} SES fresh out of the package, to a plateau of approximately 20 mN after 24 h. The cohesive forces to failure, measured using the small probe, only decreased slightly, from 15 mN to a plateau of approximately 10 mN after a 3-h exposure. The small probe induced cohesive failures for all tests, while the large probe induced adhesive failures for all tests.

4.2. *Exposure of* NEVO^{TM} *SES to Water*

The stents that were directly exposed to deionized water for up to 72 h (to further probe the impact of water uptake on adhesion and cohesion) did not exhibit any significant changes in morphology or molecular weight during such exposure. Hence, the results of the prolonged exposure were similar to those of the exposure to moisture, where the molecular weight and morphology of the NEVO^{TM} SES formulation did not change.

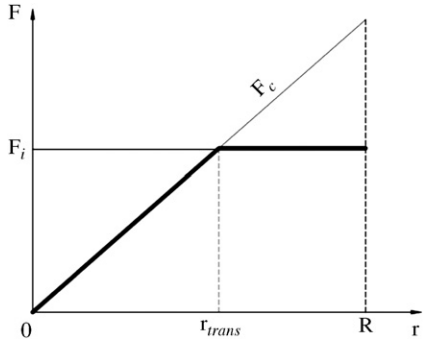

Fig. 4 – Failure modes transition.

The critical forces for failure are shown in Fig. 8. The adhesive forces decreased sharply from approximately 80 mN, for fresh out of package NEVO^{TM} SES samples, to approximately 15 mN. The cohesive forces decreased from approximately 15 mN to a plateau of approximately 10 mN, after 1 h of hydration. Again, the small probe induced cohesive failures for all tests, while the large probe induced adhesive failures for all tests.

4.3. *Exposure of* NEVO^{TM} *SES long-term hydrolysis in test tubes*

The results that were obtained from the stents that were hydrolyzed at pH 7.4 in vials containing phosphate-buffered saline for up to 60 days are presented in Figs. 5 and 9. Samples hydrolyzed longer than 60 days did not contain adequate amount of formulation in the reservoirs for adhesion tests. In any case, the molecular weight decreased gradually from 60 kDa to 30 kDa in the 2-months of hydrolysis (Fig. 5). The critical forces by the large probe are shown in Fig. 9. The critical forces decreased from approximately 100 mN to 5 mN after degradation for 60 days.

The failure modes were clearly adhesive for the samples in test tubes up to 30 days, but cohesive for samples degraded further. The reason for this could be that the polymer has degraded to an extent that not much material was left within the formulation inlay. Thus, the adhesive and cohesive strengths of the formulation have changed drastically from those under fresh conditions. Thus the large probe used did not induce adhesive failure anymore, but cohesive failure instead, for the samples degraded for long time periods.

4.4. *Long term hydrolysis in fatigue tester*

The results obtained from the stents that were subjected to cyclic loading in a fatigue tester (where hydrolysis occurred

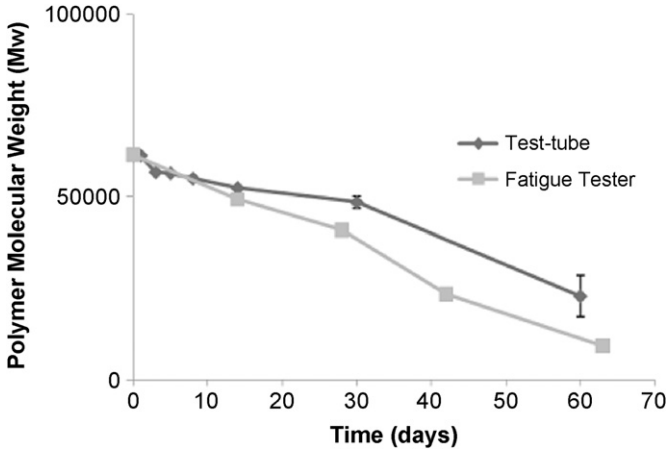

Fig. 5 – Molecular weight changes with degradation time.

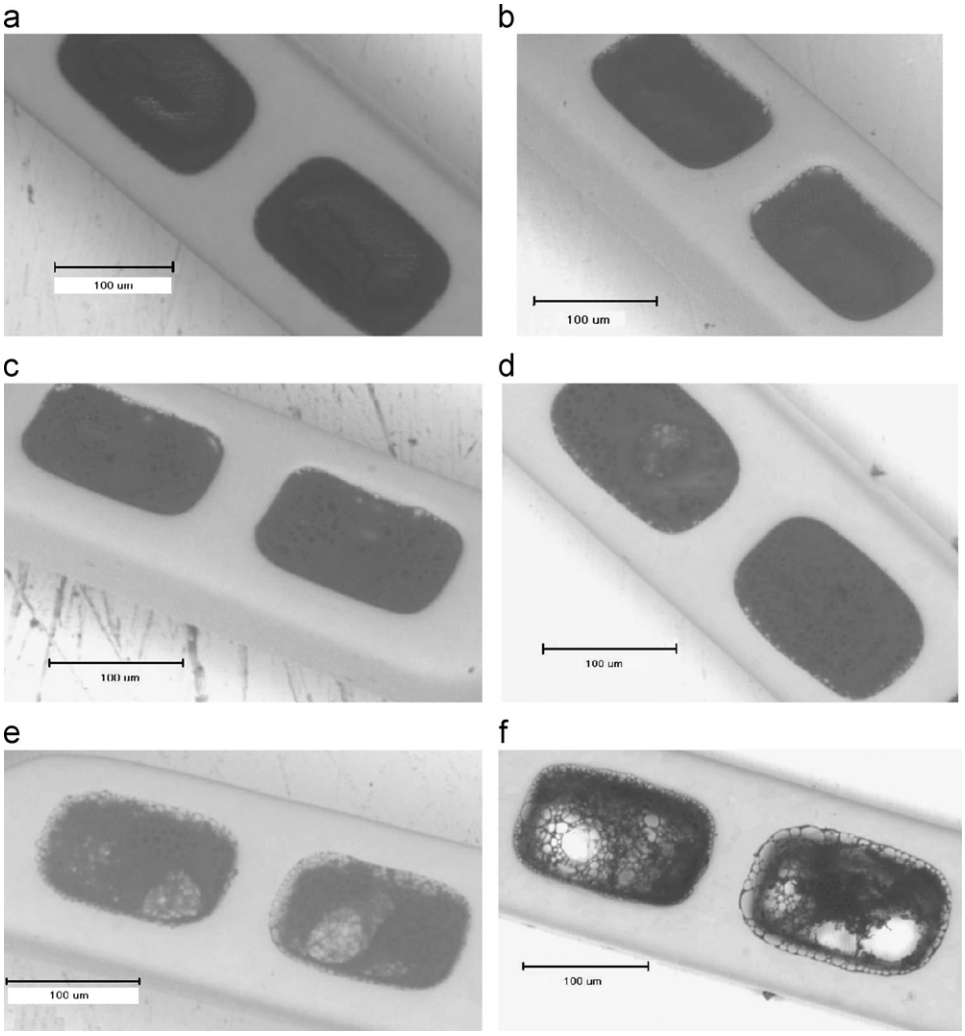

Fig. 6 – Morphology changes with degradation time (Samples in Fatigue Tester). (a) 21 days; (b) 42 days; (c) 63 days; (d) 84 days; (e) 98 days; (f) 126 days.

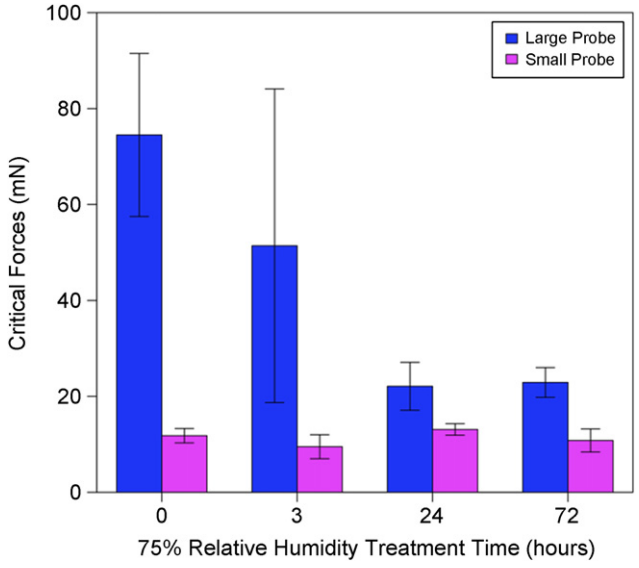

Fig. 7 – Critical forces for samples exposed to high relative humidity.

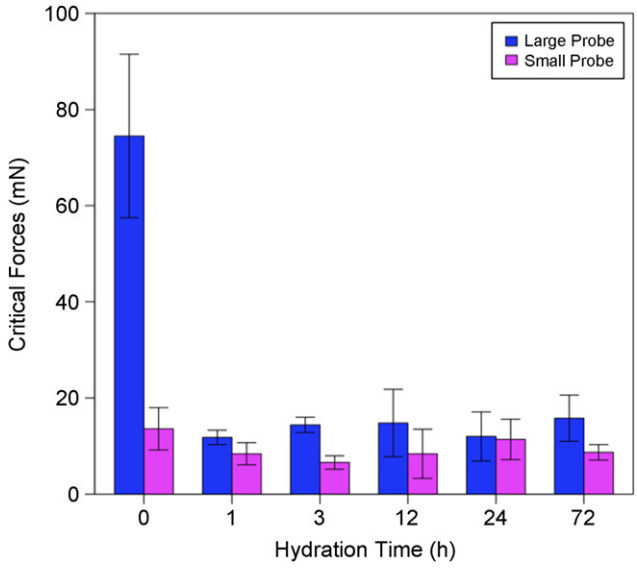

Fig. 8 – Critical forces for short-term hydrolysis samples.

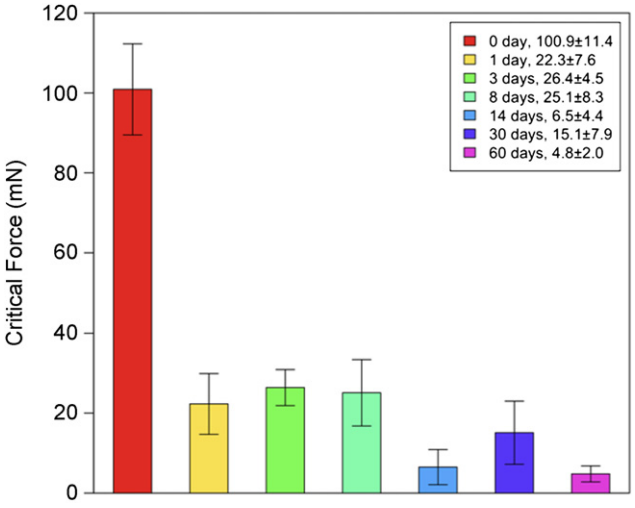

Fig. 9 – Critical forces for long-term hydrolysis samples in test tubes.

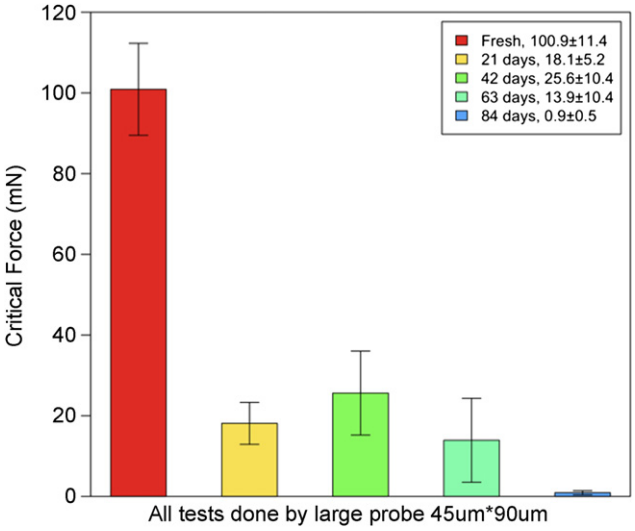

Fig. 10 – Critical forces for long-term hydrolysis samples in fatigue tester.

under mechanically loaded conditions for up to 126 days) are presented in Figs. 5, 6 and 10. Samples fatigued for longer than 84 days exhibited significant porosity in the reservoirs, generating adhesion/cohesion data below the detection limit of the tester. GPC results (Fig. 5) demonstrated that the molecular weight decreased slightly faster than the vial samples, which confirmed results of earlier studies (Fan et al., 2008).

SEM analysis showed that, during the initial 21 days, no detectable changes were observed in the morphology of the formulation (Fig. 6a). However, after 42 days, progressive pore formation and thinning in the center of the formulation were detected (Fig. 6b–f). The lag between molecular weight and morphological changes has been extensively reported in the literature (Engineer et al., 2011; Fan et al., 2008). The critical forces to failure using the large probe are plotted in Fig. 10. The critical forces decreased rapidly from approximately 100 mN when fresh, to about 18 mN after 21 days, and to 1 mN after degradation for 84 days, when the formulation inlay exhibited significant porosity (Fig. 6d).

Similar to the test tube samples, the failure modes were clearly adhesive for the samples in the fatigue tester up to 42 days, but cohesive for samples degraded further. As shown by the SEM images (Fig. 6), the polymer has degraded to an extent that not much material was left within the formulation inlay.

4.5. *Freeze–thaw cyclic thermal loading*

The force measurements from both the vial and fatigue tester studies showed profound effects of water uptake on the adhesion of the formulation to the metallic reservoir in NEVO™ SES. All samples from these two studies were preserved using nitrogen drying and freezing at −20 °C. It was important to demonstrate that these storage conditions did not impact the results. The samples were, therefore, subjected to water, and then dried with nitrogen and stored in a freezer.

To simulate extreme sample handling procedures, stents experienced up to four freeze–thaw cycles and then were tested for adhesion. The critical forces for failure measured using the large probe were plotted in Fig. 11. Hydration of fresh stents reduced the adhesion forces from 100 mN to approximately 15 mN, confirming previous results.

For samples after one freeze–thaw cycle, the forces measured were approximately 18 mN. This value was not statistically different than the value for samples that have not undergone storage. Similar to samples exposed to brief water submersion, the small probe induced cohesive failures for all tests, while the large probe induced adhesive failures for all tests. Furthermore, samples exposed to additional freeze–thaw cycles were analyzed. No practical difference was observed, as a result of additional handling. These excluded the effects of storage factor in the hydrolyzed samples from vials and the fatigue tester.

4.6. *Implications*

In this study we ensured that sample handling did not impact the adhesion/cohesion measurements. The results demonstrated that an initial exposure to water led to a significant decrease in cohesive and adhesive strengths of the NEVO™

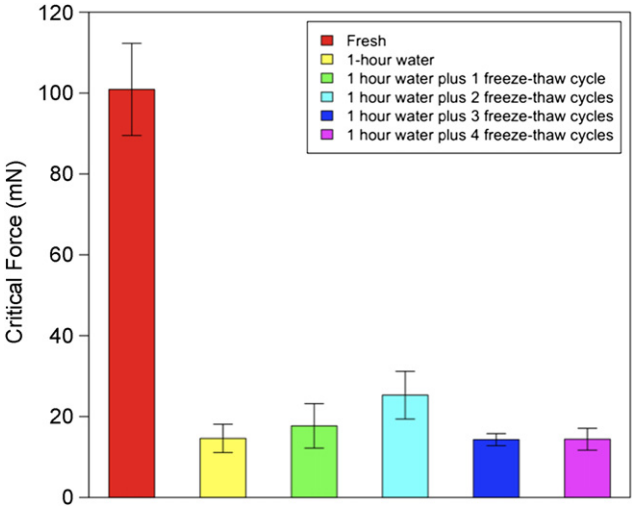

Fig. 11 – Critical force for samples undergone freeze–thaw cycles.

SES. Further exposure to water, which resulted in formulation degradation, reduced adhesive and cohesive strengths at a much slower rate. In the end, mass loss and porosity resulted in measurements below the limit of detection. The same trends were observed in stents subjected to degradation under mechanical/thermal cycling conditions. In the presence and absence of mechanical/thermal loading, comparable adhesion/cohesion results were observed.

The results showed that the decrease in mechanical strengths was primarily due to the initial exposure to water. Based on the data, it appears that water absorption had the greatest impact. Remarkably, the subsequent greater progress of ester hydrolysis, which was accompanied by dramatic morphological changes, as seen by SEM, did not seem to have a significant impact on the cohesive and adhesive strengths.

Furthermore, the application of mechanical load seemed to have little or no effect on the adhesive and cohesive strengths of the stents, even though the molecular weight decrease occurred at a faster rate. So we conclude that water absorption is the most important phenomenon.

Hence, the current results suggest that the water absorbed by the interface (between the bulk of the formulation and the metallic reservoir) played a major role in the decrease of mechanical strengths of the NEVO™ SES. This layer of water seems to bind irreversibly to the interface, as our attempts to remove the water did not result in further changes in cohesive or adhesive strengths.

5. Summary and concluding remarks

This paper presents the results of a mechanical (cohesive and adhesive) strength characterization of NEVO™ SES during the time course of formulation degradation. A micron-scale push-out testing method was used to measure the mechanical strengths. SES exposed to humidity, brief water submersion and long-term hydrolysis (with and without mechanical loading) were tested for mechanical strengths. Molecular weight and morphology changes in long-term hydrolysis were also investigated. Despite the ever-changing molecular weight and morphology, the mechanical strength loss occurred largely during the initial hours of exposure to water. The mechanical strengths then reached a plateau before decreasing ultimately to zero, as degradation of the formulation proceeded to completion.

REFERENCES

Burke, M., Clarke, B., Rochev, Y., Gorelov, A., Carroll, W., 2008. Estimation of the strength of adhesion between a thermo-responsive polymer coating and nitinol wire. Journal of Materials Science: Materials in Medicine 19, 1971–1979.

Colombo, A., Karvouni, E., 2000. Biodegradable stents: fulfilling the mission and stepping away. Circulation 102 (4), 371–373.

Engineer, C., Parikh, J., Raval, A., 2011. Effect of copolymer ratio on hydrolytic degradation of poly(lactide-co-glycolide) from drug eluting coronary stents. Chemical Engineering Research and Design 89, 328–334.

Fan, Y.B., Li, P., Zeng, L., Huang, X.J., 2008. Effects of mechanical load on the degradation of poly(D,L-lactic acid) foam. Polymer Degradation and Stability 93, 677–683.

Fattori, R., Piva, T., 2003. Drug-eluting stents in vascular intervention. Lancet 361, 247–249.

Li, Y., Bhindi, R., Khachigian, L.M., 2011. Recent developments in drug-eluting stents. Journal of Molecular Medicine 89, 545–553.

Lu, L., Peter, S.J., Lyman, M.D., Lai, H.L., Leite, S.M., Tamada, J., Uyama, S., Vacanti, J.P., Langer, R., Mikos, A.G., 2000. In vitro and in vivo degradation of porous poly(DL-lactic-co-glycolic acid) foams. Biomaterials 21, 1837–1845.

Park, T.G., 1995. Degradation of poly(lactic-co-glycolic acid) microspheres: effect of copolymer composition. Biomaterials 16, 1123–1130.

Price, G.S., Lapointe, J.M., Luk, A., Guy, G.L., SteeseBradley, G., Dooley, J., Rogers, C., 2009. Vascular safety of overlapping sirolimus-eluting reservoir technology stents in the porcine coronary artery model. Journal of the American College of Cardiology 53 (10) A74–A74.

Shan, W.L., Du, J., Hampp, E.P., Li, H., Papandreou, G., Maryanoff, C.A., Soboyejo, W.O., 2012. Adhesion and cohesion of structures containing suspended microscopic polymeric films. Acta Biomaterialia 8 (4), 1469–1480.

Soares, J.S., Moore, J.E., Rajagopal, K.R., 2010. Modeling of deformation-accelerated breakdown of polylactic acid biodegradable stents. Journal of Medical Devices 4 (4), 041007.

Strickler, F., Richard, R., McFadden, S., Lindquist, J., Schwarz, M.C., Faust, R., Wilson, G.J., Boden, M., 2010. In vivo and in vitro characterization of poly(styrene-b-isobutylene-b-styrene) copolymer stent coatings for biostability, vascular compatibility and mechanical integrity. Journal of Biomedical Materials Research A 92 (2), 773–782.

Tang, F., Ding, N., Pacetti, S. Nano-scratch adhesion evaluation of the XIENCE VTM drug eluting stent coating. Society for Biomaterials 2008 Annual Meeting.

Wolf, K.V., Zong, Z., Meng, J., Orana, A., Rahbar, N., Balss, K.M., Papandreou, G., Maryanoff, C.A., Soboyejo, W.O., 2008. An investigation of adhesion in drug-eluting stent layers. Journal of Biomedical Materials Research 87A, 272–281.