J Mater Sci: Mater Med (2009) 20:1553–1562
DOI 10.1007/s10856-009-3705-5

In vitro and in vivo evaluation of the safety and stability of the TAXUS® Paclitaxel-Eluting Coronary Stent

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Received: 19 May 2008 / Accepted: 26 January 2009 / Published online: 4 March 2009

Abstract Functional aspects of the styrene-b-isobutylene-b-styrene triblock copolymer (SIBS) which is incorporated into a drug-eluting stent (DES) coating are described. The SIBS copolymer is employed on the TAXUS® Paclitaxel-Eluting Coronary Stent as a carrier for paclitaxel (PTx). Optical and scanning electron microscopic analysis of stents explanted from rabbit and porcine models after 2 years and 6 months, respectively, showed that the SIBS coating maintained physical integrity. Gel permeation chromatography (GPC) of the copolymer extracted from the coating verified that no polymer degradation occurred over the same period of time. The coating on TAXUS® Stents was shown to maintain physical integrity after 400 million cycles of pulsatile or mechanical (tensile) fatigue, simulating 10 years real time use. Inspection of the samples compared to untested controls showed no change in the coating under these cyclic simulated conditions. Films prepared with the same formulation found on TAXUS® Stents maintained mechanical strength and resistance throughout the time of testing. Intentional defects introduced into the stent coating were shown to have only a minimal impact on PTx release. These data support the suitability of the SIBS copolymer as a drug carrier for DES applications.

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1 Introduction

Drug-eluting stents (DES) offer a minimally invasive option for the treatment of coronary artery disease (CAD) [1–6]. First generation bare metal stents (BMS) served as a scaffold to open and support occluded arteries. However, a high percentage of patients experience arterial narrowing or restenosis resulting in the need for reintervention. Local delivery of an optimized dose of a therapeutic to interrupt the complex series of events leading to restenosis is a key to the success of DES. Incorporation of the therapeutic into a coating with a polymeric carrier was shown to be an effective method to protect the drug during processing, sterilization and subsequent handling. The polymer carrier also controls the rate and duration of drug release, and provides a uniform distribution of the drug along the length of the stent.

Proper selection of the polymeric carrier is critical to the performance of a DES. The material must be compatible with the drug, be amenable to processing, sterilization, and storage, provide a means to modulate drug release, and have mechanical stability to withstand the stresses inherent in delivery and deployment. In addition, due to the unique nature of the vascular environment and the fact that this is a permanent implant, the polymer must have outstanding long term chemical and mechanical stability.

Previous publications have described the suitability of poly(styrene-b-isobutylene-b-styrene) (SIBS) copolymers for DES applications [7, 8.] The drug elution properties of SIBS have also been shown to be ideal for delivery of paclitaxel (PTx). The PTx release profile and mechanism of release have been described for the TAXUS® Stent. The majority of PTx exists as discrete particles in the SIBS matrix due to the inherent immiscibility between SIBS and PTx. Release of the PTx from SIBS can be described

primarily by the Higuchi model for a drug dispersed in a solid matrix. PTx release takes place initially from the surface of the coating. Dissolution of PTx particles adjacent to the surface may subsequently occur, however, the remaining PTx is encapsulated in the polymer matrix [7].

In this paper, the suitability of SIBS for use as a long term implant material will be described. There are many potential failure modes for a polymeric carrier, including oxidation, hydrolysis, enzymatic degradation, and acute mechanical failure. Both in vitro and ex vivo data will be presented demonstrating the stability of SIBS in a stent coating application. Data will also be presented to show that the mechanical properties of SIBS were unaltered by either the vascular environment or the repeated pulsatile motion of the vessel.

2 Materials and methods

2.1 Raw materials

The SIBS copolymer containing approximately 17 mol% styrene (130–160 K Mw/1.2–1.5 polydispersity (PDI)) was synthesized using living carbocationic polymerization using a previously described method [9, 10]. Anhydrous crystalline PTx was obtained from Indena, SpA. Milan, Italy, and was used as received. HPLC grade toluene and tetrahydrofuran (THF), used for sample preparations, were purchased from Sigma-Aldrich, Milwaukee, WI.

2.2 Degradation characterization

Samples of SIBS were thermally pretreated at temperatures ranging from 64 to 160°C for 24 h under ambient atmosphere prior to evaluation by GPC, fourier transform infrared spectroscopy (FTIR), and mechanical testing to determine thermal degradation. The molecular weight of thermally conditioned raw polymer was determined by gel permeation chromatography (GPC) using a Waters model 510 HPLC pump, model 717 autosampler, model 2410 refractive index detector and four Styragel HT columns (1-HT3, 1-HT4 and 1-HT5) calibrated using 10 narrow PDI (<1.1) polystyrene molecular weight standards (MW 1,370–2,130,000). The mobile phase was HPLC grade THF, the injection volume was 250 µl, the flow rate was 1.0 ml/min with column and detector temperatures of 35°C.

Thermally conditioned raw polymer samples were also evaluated by FTIR utilizing an attenuated total reflectance (ATR) technique. A Thermo Nicolet Nexus 670 FTIR equipped with an Endurance Foundation Series Single Bounce ATR accessory was used to generate FTIR spectra.

Mechanical testing of thermally conditioned polymers was carried out to determine the effect of accelerated aging on performance and to correlation with degradation. Films were prepared using the thermally aged raw polymer. The films were knife cast from 25% SIBS/75% solvent solutions containing a mixture of 95% toluene/5% THF. Samples for tensile testing were cut from the films using a dogbone geometry following ASTM D-1708-96-MET. Elongation at break was determined using an Alliance model RTS tensile tester.

2.3 Mechanical and pulsatile fatigue

Fatigue stability of the coating on TAXUS® Stents was assessed by evaluating the effect on both drug-loaded polymer films and coated stents. Accelerated testing carried out over 400 million cycles was used to simulate 10 years of cyclic distension in the beating heart based on a heart rate of 76 beats per minute where 1 cycle equals 1 heart beat.

Mechanical fatigue testing was carried out on an 8.8 wt% PTx/91.2% SIBS film fabricated from a THF solution using a spin casting process. The PTx loading was equivalent to the formulation used in TAXUS® Stents. The film underwent two drying cycles at 50°C for a total of 4 days to remove residual solvent. A micro dogbone was cut from the fabricated film for mechanical testing. Mechanical fatigue testing of the film was conducted using dynamic mechanical thermal analysis (DMTA) on a Rheometrics Scientific DMTA 5E (Piscathaway, NJ) at 300 cycles per second in an aqueous environment at 37°C. At the completion of the 400 million cycles of fatigue, the micro dogbone sample was removed from the DMTA and inspected by optical microscopy at 40× for evidence of cracks or internal flaws and compared to a non-fatigued control sample.

Pulsatile fatigue testing of 12 TAXUS® Express® Paclitaxel-Eluting Coronary Stents was conducted on an Endura-TEC system model 9010-4 SGT (Eden Praire, MN). The equipment was modified to create distention pulses in latex tubing containing deployed stents to exhibit fatigue in simulated vessel conditions. Three stents were expanded at a pressure of 19 atmospheres per latex tube with an ID of 3.8 mm. Five to 10 mm gaps were maintained between stents in the same tube. The stents were coated from solutions of the desired formulations using a proprietary process onto the clean surfaces of 16 mm Express® or Express^{2TM} Stainless Steel Stents (Boston Scientific Corporation, Natick, MA). The drug dose on all stents prepared was 1 µg/mm^2 PTx.

Pressurized phosphate buffered saline (PBS) containing sodium azide at 37°C was cycled through the latex tubing to simulate the conditions the stents will endure when implanted in the vasculature. Stents were cycled through 400 million cycles at a rate of 55 cycles per second. The average tubing outer diameter (OD) was measured at least every 3–4 days using a laser micrometer. Measurements of

the tubing OD and OD distention were used to determine the tubing inner diameter (ID) (equivalent to stent OD) and the stent distention. After the completion of the test, all tubes were released from the fittings and carefully returned to the unstressed condition. All stents were examined optically at 40× for structural and coating integrity and the presence of corrosion. Four coated stents were selected randomly for examination by SEM at 1,000× for the presence of cracks, breaks, or coating defects. Bare spots were examined for evidence of corrosion.

2.4 Simulated coating defect

The effect of a simulated failure in the coating integrity of TAXUS® Stents was assessed by manually creating defects in the coating and assessing the effect on drug release. Defects in the coating of 3 TAXUS® Express® Paclitaxel-Eluting Coronary Stents were created by scraping the outer surface along two longitudinal lengths of each coated stent with a scalpel.

The deformation to the stent coating was documented by photographing each stent using an optical microscope at 40× after creating the coating defects. The weight of each altered stent was determined using a microbalance before and after creating the coating defects. Individual stents were analyzed for drug release in medium (PBS-Tween 20) at 37°C using a previously published method [11.] The results were compared to the drug release profiles generated from three stents without intentionally created defects.

2.5 Rabbit iliac study

The biostability the SIBS polymer used in the TAXUS® Stent was conducted in non-injured iliac arteries of male white New Zealand rabbits at Charles River Laboratories (Southbridge, MA). All animals were pretreated with 40 mg aspirin 24 h prior to surgery and maintained daily doses of 40 mg aspirin for 30 days starting on day 2. Single 2.5 × 8 mm TAXUS® Express® Paclitaxel-Eluting Coronary Stents (Boston Scientific Corp.) were implanted in each of the common iliac arteries (left and right sides) of the animals. Clinical observations were conducted daily through out the study. Explantation of stents was performed after 2, 10, 31, 90, 181, 365, 540, and 720 days.

After dissection of the stented iliac arteries, the tissue was removed by digestion using 0.5 M sodium hydroxide (NaOH), mild heat, and mild agitation for approximately 1 week. The SIBS coating was removed from the stents and analyzed using GPC to determine molecular weight (Mn) and PDI after implantation. Non-implanted control stents from the same manufacturing lot were exposed to the tissue digestion process used on explanted stents prior to analysis by GPC. Control stents were run with each test group.

The GPC analysis was performed using a Waters Gel Permeation Chromatograph equipped with a 717 + Autosampler, 510 HPLC pump, 2410 RI Detector, and Waters Styragel HT Columns (1–100, $1–10^3$, $1–10^4$, $1–10^5$A) calibrated using polystyrene standards. The sample was eluted in HPLC Grade THF at a flow rate of 1.0 ml/min with column and detector temperatures of 35°C using an injection volume of 200 µl. Millennium software was utilized for statistical analysis.

The data was analyzed comparing the explanted stent coating molecular weight with a control using unpaired Student's *t*-test.

2.6 Porcine coronary study

An in vivo evaluation of TAXUS® Stents was conducted in non-injured coronary arteries of healthy swine at Charles River Laboratories (Worcester, MA) to demonstrate biostability of the polymer. Stents (3.0, 3.5 × 16 mm) were explanted after either 28, 60, 90 or 180 days in vivo. Arteries were bisected longitudinally. Tissue covering the bisected samples was removed by digestion using 0.5 M NaOH, mild heat, and mild agitation for approximately 1 week.

Samples were viewed using a Leo 435VP SEM with backscatter detection to highlight any bare spots and coating displacements in the TAXUS® Stent coating. In regions where it was difficult to confirm polymer coverage using backscatter detection, energy dispersive spectroscopy (EDS) was used. Representative photomicrographs of each of the stents were taken.

Following SEM analysis, the coating was removed for analysis. The molecular weight of the SIBS polymer was analyzed using GPC. Measurements were made using a Waters HPLC system equipped with a model 510 HPLC pump, model 410 differential refractometer, model 441 UV VIS detector, on-line multiangle laser light scattering (MALLS) detector (laser wavelength = 690 nm), (Mini-Dawn, Wyatt Technology Inc.), a model 712 sample processor, and five ultra-Styragel GPC columns connected in the following series: 500, 10^3, 10^4, 10^5, and 100 Å. THF was used as an eluent at a flow rate of 1.0 ml/min. The measurements were carried out at room temperature. The molecular weights and PDI was determined using ASTRA software.

3 Results and discussion

3.1 Degradation characterization

A method of analyzing ex vivo samples needed to be identified. GPC, FTIR, and mechanical testing were selected as potential candidates. The number average

molecular weight (Mn) and polydispersity index (PDI) of SIBS raw polymer samples exposed to elevated temperatures for 24 h are presented in Table 1. After 24 h at 150°C or 160°C the Mn drops 38% and 66%, respectively, and the PDI increases. There are no similar changes to the polymer aged at lower temperatures.

The corresponding FTIR results for SIBS conditioned for 24 h at temperatures ranging from room temperature to 160°C are shown in Fig. 1. Changes in the FTIR spectra of SIBS after aging at 160°C are evident in the plot. The appearance of absorbance peaks at 3,500 cm^{-1}, 1,720–1,750 cm^{-1} indicate oxidative degradation, and at 800–100 cm^{-1}indicate molecular structure reorganization These peaks have been identified elsewhere as providing evidence of thermal oxidative degradation of hydrocarbon polymers [12–14]. No changes were evident in the IR scans of raw polymer aged at temperatures up to 150°C.

Figure 2 shows the elongation at break of dogbone samples prepared from SIBS polymer aged 24 h at temperatures up to 160°C. There is no measurable change in % elongation at break for tensile dogbone samples molded with SIBS aged for 24 h up to 150°C. However, after 24 h at 160°C, the % elongation at break drops to zero. These accelerated aging studies show that changes in the properties of SIBS due to thermal degradation can be detected by mechanical testing, GPC, and FTIR. All techniques detected SIBS degradation after conditioning at similar temperatures. However, GPC was selected for examination of ex vivo samples due to the

Table 1 Molecular weight and PDI measured on SIBS raw polymer conditioned for 24 h at 25–160°C in ambient atmosphere

Temp (°C)	Mn (kg/mol)	Mw (kg/mol)	PDI
25	110	150	1.36
64	109	148	1.36
100	109	148	1.36
128	109	149	1.36
135	108	148	1.37
150	67	143	2.13
160	37	132	3.56

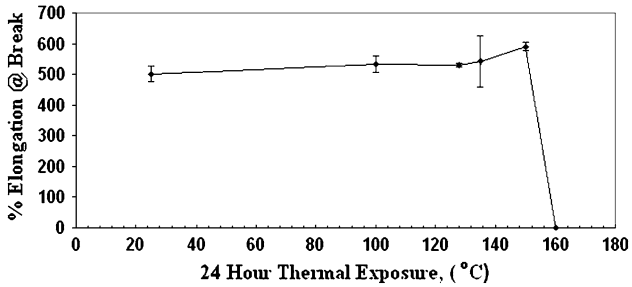
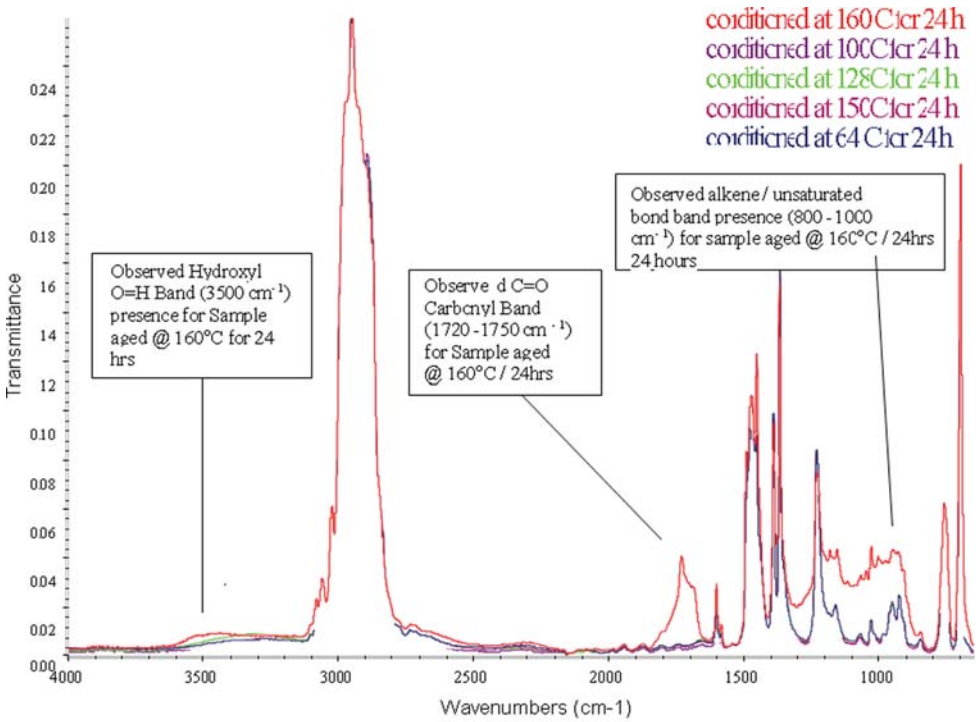


Fig. 2 Elongation at break measured on SIBS dogbone samples prepared from polymer conditioned for 24 h at 25–160°C in ambient atmosphere. Dogbones were prepared using a multilayer layer knife casting technique. Testing was performed on an Alliance model RTS tensile tester at a strain rate of 6 in/min

Fig. 1 FTIR evaluation of SIBS raw polymer conditioned in ambient atmosphere for 24 h at 25–160°C



possibility of interference in the FTIR spectra from adsorbed proteins in an ex vivo analysis. In addition, suitable geometries for mechanical analysis ex vivo arterial samples would be difficult to obtain.

3.2 In vitro characterization

In vitro evaluation of the TAXUS® Stent as well as films representing the coating are meant to predict the stability of the coating to cyclic loading as well as to deformation that could affect the coating after crossing a calcified coronary lesion.

3.3 Mechanical and pulsatile fatigue

Two studies examined the mechanical integrity of the SIBS/PTx formulation over 400 million cycles to simulate 10 years of cyclic distension in the beating heart. The mechanical behavior of the 8.8% PTx/91.2% SIBS polymeric film during mechanical fatigue testing is depicted in Fig. 3 and Table 2. A PTx/SIBS film was determined to be representative of the TAXUS® Stent coating. A frequency of 300 Hz was selected both to decrease test time and as a worst case scenario. In a separate frequency sweep (data not shown), the modulus of the SIBS polymer was shown to be significantly higher at 300 Hz than at 55 Hz. Therefore, at a given strain, the polymer is exposed to greater fatigue stress when tested at higher frequencies. The tensile modulus of the film varied less than 4.4% from the average over the 400 million cycles of the test. An increase or decrease in modulus (greater than 10–15% depending on the polymer and test conditions) could indicate a morphological change related to the fatigue process, such as molecular orientation (strain hardening), crazing, or crack formation and propagation. In addition, the PTx/SIBS test dogbone specimen maintained physical integrity after 400

Table 2 Force and strain values at 50 million cycle intervals measured during dynamic mechanical fatigue testing of PTx/SIBS films

Time (s)	Cycles at 300 Hz	Force (*g*)	Bath temperature (°C)	Strain (actual)
1006	301,800	2750.6	37.173	1.0023
166,690	50,007,000	2849	37.297	1.0009
333,370	100,011,000	2836.5	37.179	0.99343
500,060	150,018,000	2865.5	37.207	0.99876
666,080	199,824,000	2871.5	37.22	0.99682
833,430	250,029,000	2875.6	37.271	0.99849
1,000,100	300,030,000	2896.1	37.286	1.0033
1,166,800	350,040,000	2886.7	37.26	0.99886
1,333,500	400,050,000	2878.6	37.242	0.99564
1,354,900	406,470,000	2871.7	37.194	0.99184

Test conditions: 1% cyclic strain, 300Hx cyclic frequency, and 400 million cycles, aqueous environment at 37°C. Sample: micro dogbone (5.8 mm long × 2.2 mm wide × 0.44 mm thick)

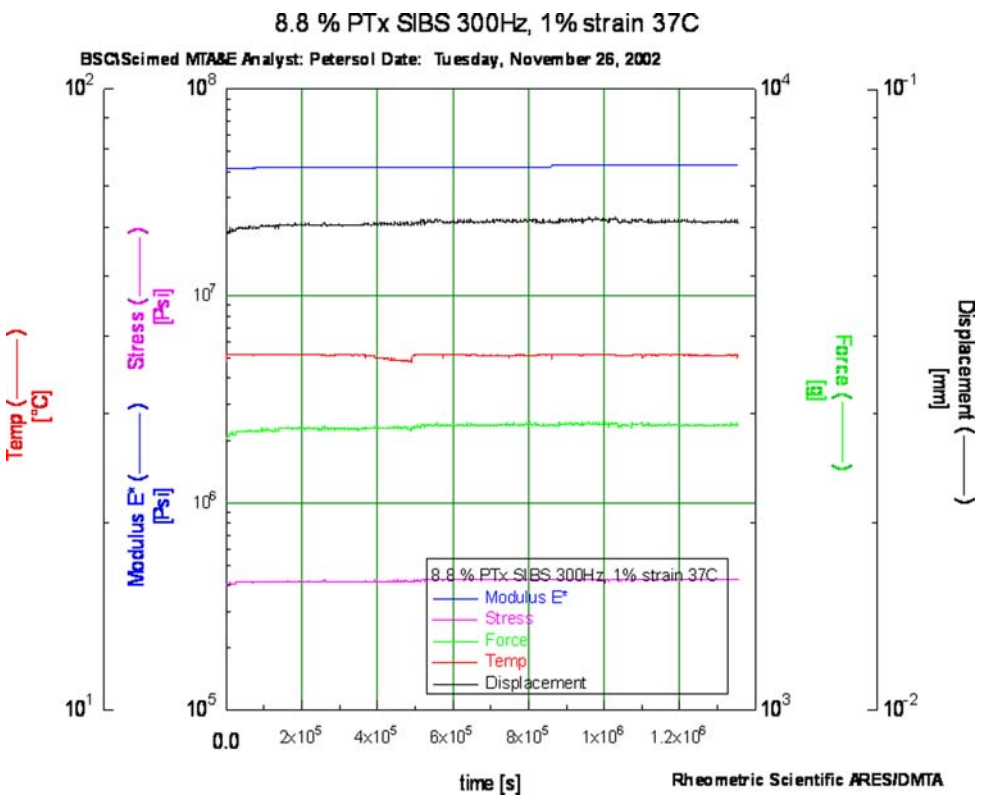


Fig. 3 Mechanical behavior of a PTx/SIBS film during mechanical fatigue testing. Test conditions: 1% cyclic strain, 300Hx cyclic frequency, and 400 million cycles, aqueous environment at physiologic temperature (37°C). Sample: micro dogbone (5.8 mm long × 2.2 mm wide × 0.44 mm thick)

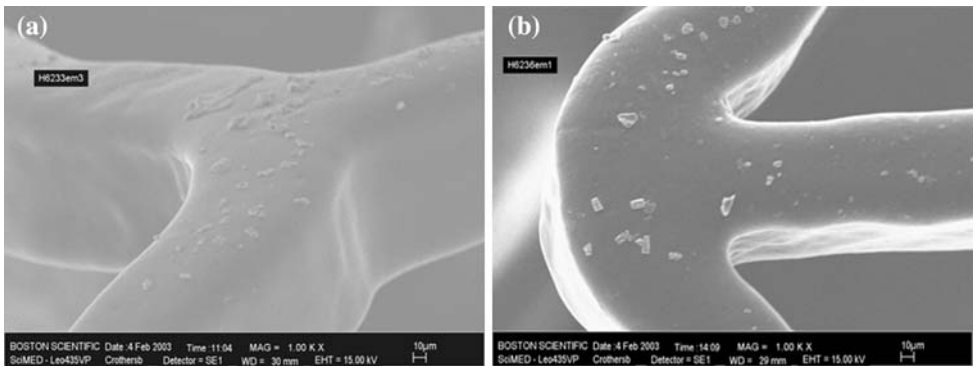


Fig. 4 SEM images of TAXUS® Express® Paclitaxel-Eluting Coronary Stents during pulsatile fatigue testing. Four randomly selected stents examined at a minimum of eight locations at 1,000×. Presence of salt from the media is present on the stent surface

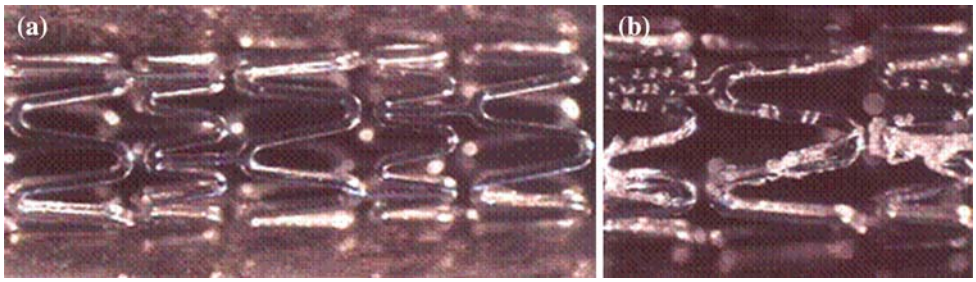


Fig. 5 Optical microscope images of TAXUS® Express® Paclitaxel-Eluting Coronary Stents before (**a**) and after (**b**) manually creating defects in the coating. Defects were created along the entire length of opposite sides of the stent

million cycles, with no evidence of catastrophic failure or localized yielding. Visual inspection revealed no evidence of mechanical breakdown such as micro-cracks, crazing, catastrophic failure, or formation of internal voids after 400 million cycles of fatigue testing.

Coated TAXUS® Stents exposed to pulsatile fatigue testing for 400 million cycles show the physical stability of the actual SIBS/PTx coating. After testing the examined stents showed defect levels comparable to untested stents. No defects, such as cracked or broken struts, were observed using an optical microscope. The coating quality of the tested stents showed no change relative to the coating of untested control stents. In addition, there was no indication increased level of coating deformation or corrosion on the stent surface after testing.

Representative images of the four coated stents selected for SEM examination are presented in Fig. 4. The coating surfaces depicted in the images show no presence of cracks, breaks, or coating defects. No evidence of corrosion was found after examination of the bare spots. Note the presence of salt crystals from the saline solution used in the pulsatile fatigue tester.

3.4 Simulated coating defect

The results of accelerated in vitro studies suggest that the TAXUS® Stent SIBS polymer coating will not exhibit mechanical breakdown or failure under anticipated vascular fatigue conditions. Deformations made to the stent surface by deliberately introducing a significant coating defect resulted in the coating rolling onto itself as the bare stent was exposed as shown in Fig. 5. Although a limited section is shown, surface defects on the abluminal surface of the stent extended over the entire length. In some cases, the metal surface of an entire stent strut was exposed due to the coating deformation; however, the adjacent coating material remained adhered to the stent struts. Ridges of material formed on and between the stent struts. In some cases the damage extended to the lumenal strut surfaces. By visual estimation, 50% of the coating on the outer surface of the stent was damaged using this process with additional damage to adjacent surfaces.

Stent weights obtained before and after creation of the simulated coating defects indicate that no coating material was lost during the scraping process as shown in Table 3. As the coating accumulated in areas along the stent, minimal increase in the PTx release rate was measured, as shown in Fig. 6. The increase in PTx release may be due to exposure of additional drug/polymer surface area. After 10 days' exposure to release medium, the stents containing

Table 3 The weight of TAXUS® Express® Paclitaxel-Eluting Coronary Stents before and after manually creating defects in the coating

Stent ID	Weight (mg)	
	Final coating weight (before)	After creating breach
A	21.519	21.521
B	22.547	22.549
C	23.328	22.320

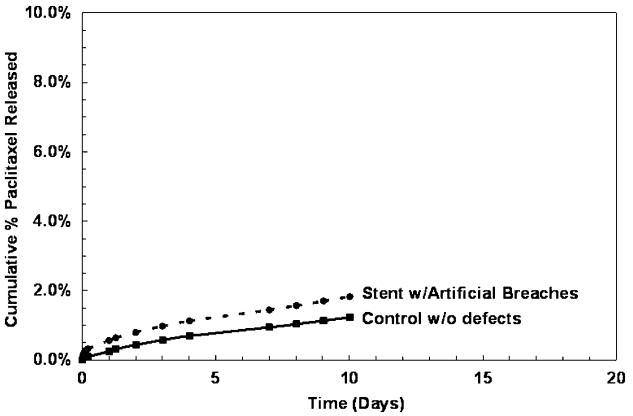


Fig. 6 Percent cumulative paclitaxel release from TAXUS® Express® Paclitaxel-Eluting Coronary Stents with simulated coating breaches

catastrophic defects released 1.8% of the loaded PTx compared to 1.2% released from unaltered controls. The total amount of drug released corresponds to 1.9 and 1.3 μg, respectively. The small increase in PTx release indicates that the coating did not fragment, but maintained its integrity after the high degree of damage. In addition, the 1.9 μg released over 10 days is well below the amount released from the TAXUS® moderate release formulation, which was tested in the Taxus II clinical trial and shown to be safe and effective for the treatment of CAD [15].

SIBS is a thermoplastic elastomer, (TPE) owing its mechanical properties to phase separation of the two incompatible copolymer blocks. The rubbery isobutylene blocks make up the bulk of the coating, providing flexibility, and the glassy (at room temperature) styrene domains provide rigidity in the form of physical crosslinks. The unique structure also imparts the ability to dissipate energy as would occur by scraping the coating down to the stent surface. The result is that the polymer can be deformed to the point of tearing, but retains its overall integrity and is not lost from the coated surface. In general, TPEs are well suited for use as a stent coating, where fatigue and/or physical challenges such as crossing calcified lesions could lead to coating failure.

3.5 In vivo characterization

In vivo evaluation of the TAXUS® Stent was performed to determine the biostability of the SIBS coating as well as the overall integrity of the coated stent to the in vivo environment.

3.6 Rabbit iliac study

The molecular weight of SIBS associated with TAXUS® Stents implanted in rabbit iliac arteries compared to non-implanted stents was used to assess the long term biostability of SIBS. The rabbit provided a small adult animal model that could easily be maintained out to 2 years. The Mn and PDI of SIBS removed from stents explanted after 2–720 days and the corresponding controls are shown in Table 4. No indication of polymer degradation or break down was detected based on these results. The Mn of SIBS ranged from 100 to 106 K throughout the duration of the implant. No statistical difference in both Mn and PDI was measured between day 0 and values measured on SIBS at all explanted time points ($P > 0.05$). A value less than 0.05 indicates a statistical difference between the control and test samples.

Figure 7 compares GPC chromatograms for SIBS polymer removed from the stents implanted for 360 days and the control SIBS sample The chromatograms appear similar, indicating no change in Mn or PDI of the polymer during exposure to tissue blood. Similar GPC chromatograms were observed at all timepoints.

3.7 Porcine coronary study

The effect of in vivo conditions on the coating integrity and molecular weight of the SIBS polymer on TAXUS® Stents was evaluated in porcine coronary arteries. The porcine coronary model was used to confirm and extend the observations from the long term rabbit study to the coronary anatomy. In addition, it is a well-accepted model for examination of the vascular response to coated stents [16]. The study matrix and results are given in Table 5. The elution time for the primary peak in the GPC analysis was identical for the reference polymer and test samples, indicating that the major fraction of the explanted SIBS polymer has the same Mn and PDI.

Table 4 Number average molecular weight (Mn) and polydispersity index (PDI) of the SIBS polymer removed from TAXUS® Express® Paclitaxel-Eluting Coronary Stents that were implanted in rabbit iliac arteries for up to 720 days

Days in vivo	Sample size	Mn (kg/mol)	SD	*P*-value	PDI	SD	*P*-value
0	14	103	2.7	N/A	1.39	0.02	N/A
2	6	100	0.6	0.594	1.40	0.01	0.198
10	6	100	0.4	0.940	1.41	0.01	0.665
31	6	100	0.4	0.688	1.40	0.01	0.342
90	6	104	7.9	0.342	1.37	0.06	0.390
181	6	100	0.4	0.889	1.40	0.01	0.737
365	6	100	0.3	0.199	1.40	0.01	0.342
540	8	105	1.7	0.333	1.38	0.02	0.253
720	14	106	2.2	0.198	1.38	0.02	0.590

T-Test *P*-values based on unpaired, two-tailed analysis versus day 0 values. SD = one standard deviation. Values are the average of the results from three injections

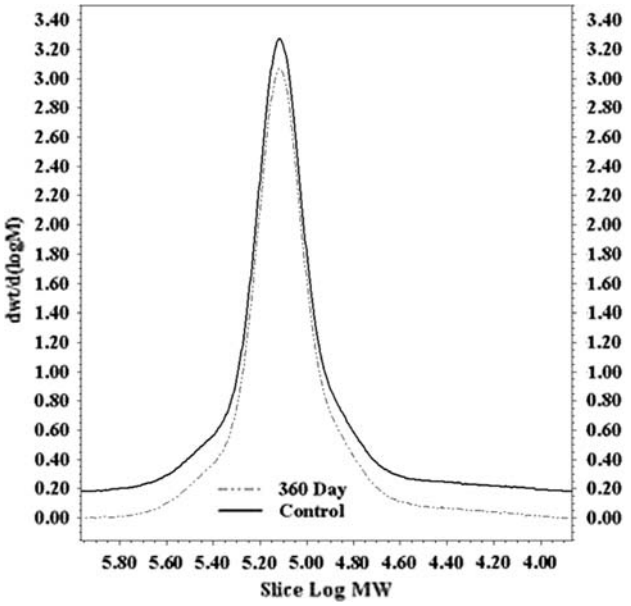


Fig. 7 GPC chromatograms for SIBS polymer removed from explanted TAXUS® Stents after 360 days in rabbit iliac arteries compared to the control SIBS. Similar GPC chromatograms were observed at the 90 and 180 day timepoints

Table 5 Average Mn of the SIBS polymer removed from TAXUS® Paclitaxel-Eluting Coronary Stents that were implanted porcine coronary arteries for up to 180 days

Time period	# Stents	Mn (kg/mol)	PDI
28	1	130	1.32
60	3	135	1.32
90	1	137	1.30
180	3	133	1.33

Duplicate GPC runs for each stent except on one stent in 180 days group due to insufficient levels of polymer

Representative SEM images of stents explanted after 90 and 180 days are shown in Fig. 8. SEM examination of all explanted stents indicated that the coating covered the entire stent and maintained visual uniformity along the length of the stent. No visible cracking or delamination of the conformal coating was detected. The occasional bare spots and coating defects observed were similar in quantity and size to those seen on expanded TAXUS® Stents that were not implanted as shown in Fig. 9. No visible differences were noted between the ID and OD of any test stents. Figure 10 compares the coating quality observed by SEM on the inside diameter (ID) and outside diameter (OD) of a stent.

Potential failure mechanisms of a polymeric drug carrier used as a long term implant include hydrolysis, thermal degradation, and enzymatic attack. In addition, physical stresses resulting from expansion of the stent and cyclic distention in the beating heart could accelerate mechanical or fatigue failure of the polymer. Absorption of biological fluids may result in plasticization or antiplasticization of the polymer with subsequent changes in chemical or physical behavior. Results from both the porcine and rabbit studies demonstrate that the molecular weight distribution of SIBS did not change when exposed to the in vivo environment for up to 2 years. In addition, the results

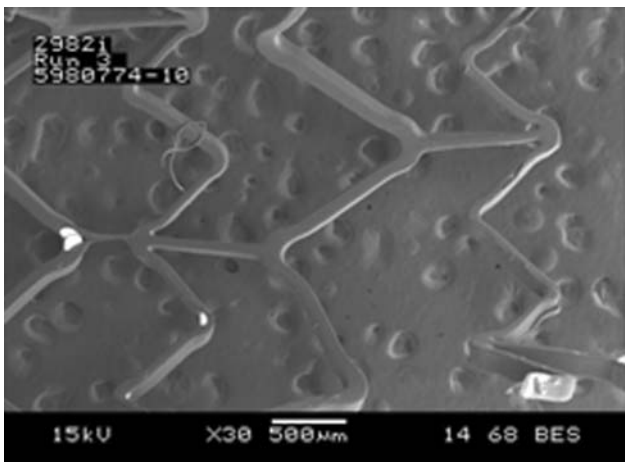


Fig. 9 SEM image of a TAXUS® Express® Paclitaxel-Eluting Stent that was not implanted showing representative bare spots or coating displacements

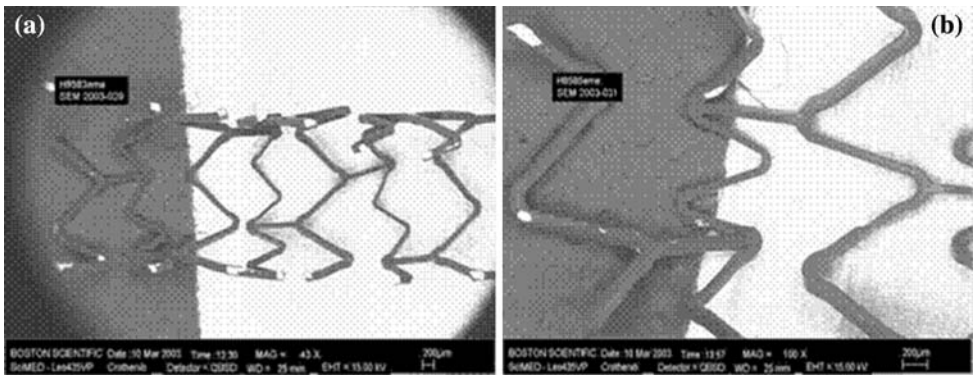


Fig. 8 Representative SEM images of TAXUS® Stents explanted after **a** 90 days (43×) and **b** 180 days (100×) implanted in porcine coronary arteries. Bisection artifacts from longitudinal cutting of the stent are visible in image

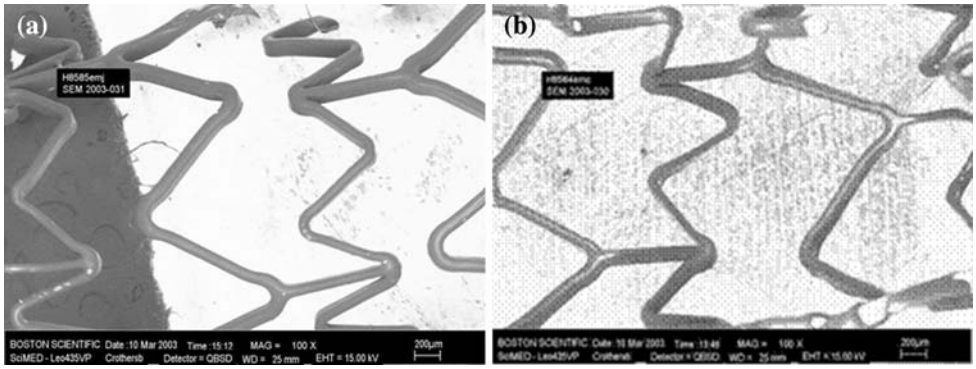


Fig. 10 Representative SEM images of the **a** interior (ID) and **b** exterior (OD) of TAXUS® coated stents explanted after 180 days in a porcine coronary artery

demonstrate that the mechanical properties of the SIBS copolymer are appropriate for stent coating applications.

4 Conclusions

The stability of the TAXUS® Stent was evaluated by investigating the fatigue resistance (pulsatile and DMA) and the in vivo biostabilty in two different animal models. The excellent in vivo biostability was demonstrated through examination of stents and the SIBS polymer associated with stents implanted in porcine coronary and rabbit iliac arteries. Explanted stents from the studies showed identical coating characteristics compared with controls that were expanded and not implanted. Circumferential and longitudinal coating uniformity was maintained without compromise and no cracking, flaking, delamination or visual evidence of degradation was noted in the ex vivo samples. In addition, GPC analysis of the polymer coating indicated that no degradation of the molecular weight had occurred up to 180 days in porcine coronary and 720 days in rabbit iliac arteries.

While implanted, stents are subject to cyclic forces that may promote mechanical breakdown resulting in stent or coating failure in the vasculature. During in vivo testing, the coating on TAXUS® Stents was shown to maintain physical integrity after 400 million test cycles which translates to an estimated real time of 10 years of cyclic distention. Similarly films prepared with the same formulation found on TAXUS® Stents maintained mechanical properties during cyclic testing without showing visual indications of mechanical failure. The combined mechanical and pulsatile fatigue data supports the physical stability of the SIBS/PTx coating under sustained mechanical cyclic stress.

The impact of an unlikely coating failure on PTx release from TAXUS® Stents was also investigated and found to be minimal. In addition, the TAXUS® Stent coating demonstrates a high affinity for itself and the stent. The data presented here demonstrates the long term biostability, mechanical stability and integrity of the SIBS polymer used in the TAXUS® Stent formulation, under stressed conditions in vitro and in vivo.

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