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Review

Medical applications of poly(styrene-*block*-isobutylene-*block*-styrene) (“SIBS”)

Leonard Pinchuk[a,*], Gregory J. Wilson[b], James J. Barry[c], Richard T. Schoephoerster[d], Jean-Marie Parel[e,f], Joseph P. Kennedy[g]

[a]*Innovia LLC and InnFocus LLC, 12415 SW 136 Ave Unit 3, Miami, FL 33186, USA*
[b]*The Hospital for Sick Children, Toronto, Ontario, Canada*
[c]*Boston Scientific Corporation, Natick, MA, USA*
[d]*Florida International University, Miami, FL , USA*
[e]*Ophthalmic Biophysics Center, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA*
[f]*University of Liege, CHU Sart-Tilman, Liege, Belgium*
[g]*The University of Akron, Akron, OH, USA*

Received 13 July 2007; accepted 30 September 2007

Abstract

Poly(Styrene-*block*-IsoButylene-*block*-Styrene) (“SIBS”) is a biostable thermoplastic elastomer with physical properties that overlap silicone rubber and polyurethane. Initial data collected with SIBS stent-grafts and coatings on metallic stents demonstrate hemocompatibility, biocompatibility and long-term stability in contact with metal. SIBS has been used successfully as the carrier for a drug-eluting coronary stent; specifically Boston Scientific’s TAXUS® stent, and its uses are being investigated for ophthalmic implants to treat glaucoma, synthetic heart valves to possibly replace tissue valves and other applications. At present, researchers developing medical devices utilizing SIBS have found the following: (1) SIBS does not substantially activate platelets in the vascular system; (2) polymorphonuclear leukocytes in large numbers are not commonly observed around SIBS implants in the vascular system or in subcutaneous implants or in the eye; (3) myofibroblasts, scarring and encapsulation are not clinically significant with SIBS implanted in the eye; (4) embrittlement has not been observed in any implant location; (5) calcification within the polymer has not been observed; and (6) degradation has not been observed in any living system to date. Some deficiencies of SIBS that need to be addressed include creep deformation in certain load-bearing applications and certain sterilization requirements. The reason for the excellent biocompatibility of SIBS may be due to the inertness of SIBS and lack of cleavable moieties that could be chemotactic towards phagocytes.

Keywords: Biostable; Poly(styrene-*b*-isobutylene-*b*-styrene); SIBS; Glaucoma; Polyurethane

Contents

*Corresponding author. Tel.: +1 305 378 2651x284; fax: +1 305 378 2652.
E-mail address: len@innovia-llc.com (L. Pinchuk).

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doi:10.1016/j.biomaterials.2007.09.041

1. Introduction

Poly(Styrene-*block*-IsoButylene-*block*-Styrene) (''SIBS'') was relatively unknown in medicine prior to the introduction of Boston Scientific Corporation's (BSC) (Natick, MA) Drug Eluting TAXUS® Coronary Stent in 2002. This medical device has significantly reduced the incidence of coronary bypass procedures and associated morbidities. SIBS is a thermoplastic elastomer whose physical properties overlap both the silicone rubbers and polyurethanes. SIBS is oxidatively, hydrolytically and enzymatically stable over its lifespan in the body and is, therefore, biostable with a relatively low foreign body reaction.

The development of SIBS for medical devices evolved from deficiencies encountered with the long-term *in vivo* performance of polyurethanes; specifically, their degradation and concomitant inflammatory and fibrotic reactions. These deficiencies limited the use of polyurethanes for long-term load-bearing implant applications and for applications in contact with metal, as metal ions contribute to polyurethane degradation by oxidative pathways. It is important to understand these nuances to appreciate the significance of the polymer chemistry of SIBS; a brief review of the use of polyurethanes in the body will therefore also be presented.

The inertness of SIBS has enabled novel medical devices, such as the aforementioned TAXUS® Stent, a minimally invasive glaucoma drainage tube implant for treating glaucoma (Miami-Innfocus Drainage Implant—''MIDI-Tube'') and a synthetic trileaflet aortic valve to possibly replace tissue and mechanical valves. Several other medical devices made from SIBS are in early stages of development, e.g., spinal implants, and may be commercialized over the next few years.

2. The degradation of polyurethanes and events leading to SIBS

In the early 1980s, Medtronic Corporation (Minneapolis, MN) introduced the polyether urethane-insulated pacemaker lead. The polyurethane was manufactured by Dow Chemical and sold as Pellethane® 2363 80A, a thermoplastic aromatic polyether urethane. By the mid-1980s, reports describing surface pitting and cracking of the polyether urethane lead insulator began appearing in the literature. In the early 1990s, the degradation of these polyurethanes became widespread and represented the limiting factor in the development of novel medical devices using microfilamentous scaffolds requiring load-bearing properties, such as compliant vascular grafts (see Fig. 1A). A review of the state-of-the-art of polyurethanes in the mid-1990s was presented by Pinchuk [1]. Contrary to what had been reported in the literature [2], these microfilamentous polyurethanes did not need to be stressed to exhibit biodegradation. Simple relaxed subcutaneous implants of these microporous high surface area materials in animals showed significant biodegradation in less than 4 weeks. This implant model was used to investigate a variety of polyurethanes with soft segments including polydimethylsiloxane (PDMS) diols and fluorinated PDMS diols. In addition, surface treatment of conventional polyurethanes, such as with plasma polymerized polytetrafluoroethylene (PTFE) and surface-grafted PDMS, were also investigated [3,4]. It was found that surface treatment or surface grafting, did not protect the polyurethane from biodegradation as, in the case of PTFE coatings, they cracked due to compliance mismatch thereby exposing the underlying polyurethane to the surrounding bodily fluids. Although degradation was delayed for months by the use of surface-grafted PDMS, this coating was sufficiently oxygen permeable to enable oxidation of the underlying polyurethane. A variety of polyurethanes with various soft segments containing PDMS and surface modifying agents have appeared in the literature over the last decade; however, these materials exhibited similar biodegradation [5–11].

The degradation mechanism of polyether urethanes was elucidated by Anderson's group [12,13] at Case Western Reserve University (Cleveland, Ohio). They found that the carbon alpha to the ether of the polyether soft segment was oxidized to ester either by superoxide produced by polymorphonuclear leucocytes (PMNs) and the like, or by metal ion contact of the polyurethane, as occurs on the inside of pacemaker lead insulators. Subsequent hydrolysis of the ester cleaves the macromolecule, and in the presence of flexion, cracks develop. Realizing that the ether groups were vulnerable, Pinchuk introduced more biostable polycarbonate urethanes for implant applications which were initially commercialized under the trade name: Corethane™ (Corvita Corp., Miami, FL (acquired by Boston Scientific Corporation, Natick, MA)) [14,15]. The polycarbonate urethane patents were transferred to the Polymer Technology Group (Berkeley, CA) in 1996 and various formulations of these polyurethanes are currently being marketed under the trade name ''Bionate''.

The motivation to develop biostable polyurethanes stemmed from the need for elastomeric materials to provide compliant vascular grafts as well as deformable

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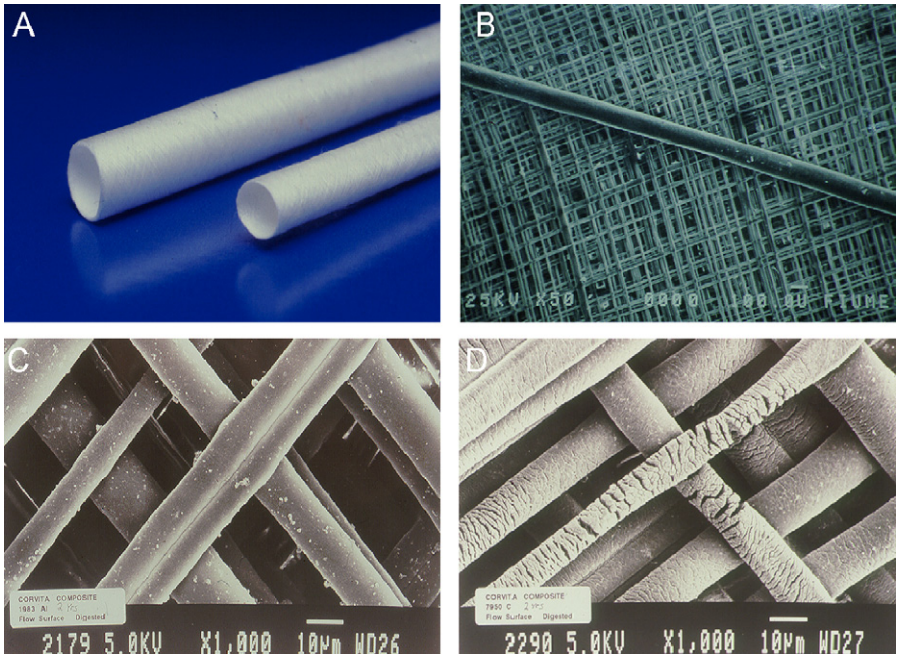

Fig. 1. (A) Non-implanted spun tubular meshwork vascular graft. (B) SEM of the graft showing 10 μm diameter polycarbonate urethane fibers as compared to a human hair (shown on the diagonal). (C) Meshwork at 2 years explant showing a virtually intact fibrous structure. (D) Numerous fibers of the same graft demonstrating surface cracking.

stent-graft liners [16–18]. The improved biostability of polycarbonate urethanes was confirmed by Stoke's group at Medtronic using the "Stokes Test", in which a tube of the material is stretched over a dumbbell-shaped mandril and exposed to oxidizing and hydrolyzing chemicals, or is implanted in the body for a predetermined time [19]. Materials that are readily susceptible to oxidation and hydrolysis crack in this model; significantly, the polycarbonate urethanes did not crack.

Although polycarbonate urethanes demonstrated superior biostability relative to the polyether and polyester urethanes, they too eventually exhibited biodegradation as manifested by surface cracking. Fig. 1 shows a scanning electron micrograph (SEM) of a spun-polycarbonate urethane aorto-iliac vascular graft explanted from a dog at 2 years. Fig. 1A shows the non-implanted spun tubular meshwork; Fig. 1B is an SEM of the graft showing the polycarbonate urethane microfibers (diameter approximately 10 μm) in comparison to a human hair (Fig. 1B) which is 10 times larger in diameter. Fig. 1C is an explant of the polycarbonate urethane meshwork at 2 years showing the fibrous structure virtually intact, whereas Fig. 1D shows numerous fibers of the same graft demonstrating surface cracking. The fractures were most noticeable in areas with large numbers of macrophages on histology (not shown).

Importantly, Wilson's group (The Hospital for Sick Children, Toronto, Ontario) also observed that these degrading implants attracted a plethora of PMNs, especially during the early weeks of implantation (Fig. 2A). Further, the cleaner the polycarbonate urethane (less extractables, washed surfaces), the more intense the inflammation. Further observations were the attraction of macrophages, foreign body giant cells and the phagocytosis of small "chunks" of polyurethane (Figs. 2B and C). Lastly, it was also observed upon careful examination that crack formation in the microfilamentous grafts occurred in areas of the graft as early as 1 month after implantation.

In summary, polyurethanes exhibit degradation with time with signs of the problem occurring within weeks of implantation. Degradation is due to oxidation, most likely by superoxide produced by phagocytes ("scavenger cells"); the more degradation, the greater number of scavenger cells that migrate to the site to engulf and therefore sequester the eluting material. Because phagocytes release substances which stimulate fibrosis, the eluting material becomes encapsulated; that is, walled off. By the mid-1990s, it became apparent that new polymers were needed for medical devices that required long-term implantation for load-bearing applications. This was particularly essential in microporous embodiments as well as in products utilizing metals, such as stents, stent-grafts, drug-eluting stents and pacer leads.

3. The SIBS hypothesis

An analysis of the degradation mechanism of polyurethanes combined with an understanding of organic chemistry principles led to the hypothesis that the long-term stability of a polymeric material in living tissue can be achieved when both the polymeric backbone and pendant groups are devoid of unprotected ester, amide, ether,

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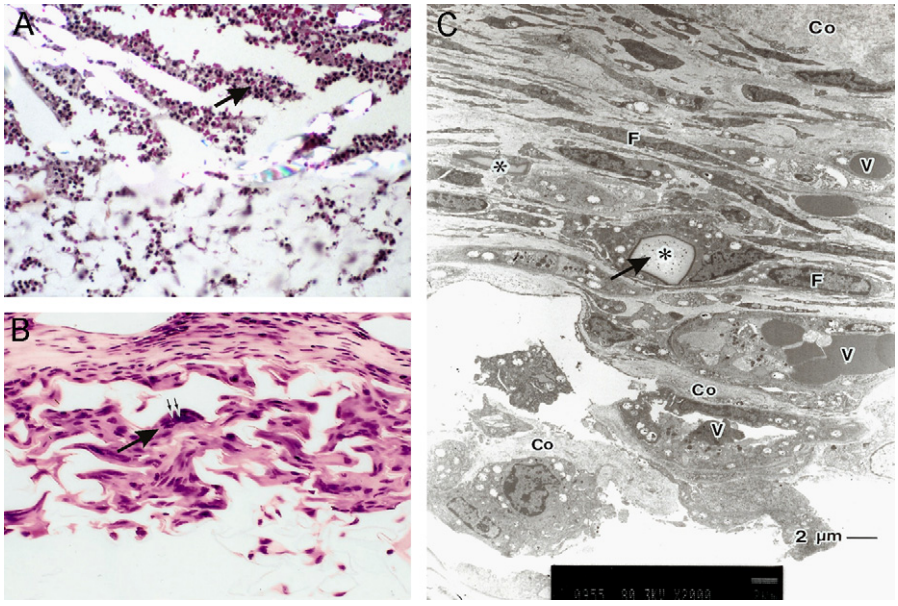

Fig. 2. The arrows point to: (A) polymorphonuclear leukocytes around an 8-week subcutaneous implant of a polycarbonate urethane in a dog (unpublished work courtesy of G. Wilson, The Hospital for Sick Children, Toronoto Ontario Canada); (B) foreign body giant cells in a 12-week polyurethane implant intrastromal in the cornea of a rabbit eye; (C) phagocytosis of a polyurethane by foreign body giant cells in a 21-week intrastromal implantation in the cornea of a rabbit eye (B and C are provided courtesy of M. Fukuda et al.; Kinki University School of Medicine, Osaka, Japan).

carbamate, urea, or any other groups that are prone to oxidation, hydrolysis, or enzymatic cleavage. Further, the degradation of polyethylene acetabular joint liners that produce in-chain unsaturation and crosslinking [20–23], that dominated the literature for the last two decades, suggest that secondary carbon-containing polymers such as polyethylene, and secondary-and-tertiary carbon-containing polymers such as polypropylene [24–26], are also to be avoided as double bond formation leads to embrittlement and stress cracking. It must also be kept in mind that, depending on the polymerization processes used, polyethylene always contains a number of methyl (or higher alkyl) branches, and therefore contains a corresponding number of oxidizable tertiary hydrogens (~C**H**(CH_3)CH_2~). These irregularities are not protected within the polyethylene crystallites, and, particularly when exposed on surfaces, are accessible to oxidative attack by the body's defense systems.

Consequently, it was hypothesized that an ideal polymer for implant application should contain only oxidatively, hydrolytically and enzymatically stable alternating secondary-and-quaternary carbons in the backbone, and equally stable primary carbons as pendant groups. The basic structures of this nature are those comprised of polyisobutylene (PIB) shown on the left of Fig. 3. The absence of cleavable side groups in PIB, in contrast to potentially hydrolyzable ester groups in methacrylate polymers, e.g., the methoxy group in poly(methylmethacrylate), shown on the right of Fig. 3, which contains a similar alternating secondary–quaternary carbon backbone, should provide a polymer with less biodegradation. Further, if this hypothesis is correct, the less biodegradation, the less inflammation.

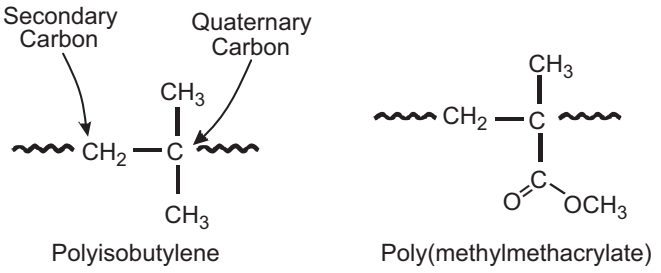

Fig. 3. Schematic of polyisobutylene with its alternating secondary and quaternary carbons and lack of labile pendent groups as compared to poly(methylmethacrylate) with its ester side group.

PIB, an inert non-vulcanizable rubber used in many industrial applications (i.e., tackifiers, adhesives, sealants, thickening agents, viscosity enhancers, various additives, chewing gum, etc.) can be obtained easily and inexpensively by the cationic polymerization of isobutylene. However, PIB cannot be used in applications where shape retention is essential because it is not crosslinked. A very close relative to PIB is butyl rubber, a commercially available copolymer of ~98% isobutylene and ~2% isoprene, in which the few but critically important isoprene units $–CH_2–C(CH_3)=CH–CH_2–$ provide vulcanizability, that is shape retention. However, butyl rubber is also unsuitable for implantation in living tissue as: (1) it contains oxidatively vulnerable unsaturations, and (2) it can be converted into a shape-retaining rubber only by vulcanization under harsh, biologically unacceptable, conditions with crosslinkers and additives that are generally not tolerated in the body.

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The search for PIB-based thermoplastic elastomers, i.e., for elastomers that contains PIB rubbery segments covalently linked to readily thermally- and/or solution-processible glassy segments, led the lead author to Kennedy's laboratory at The University of Akron where such polymers were already synthesized [27]. Kennedy's patents protecting the triblock copolymer SIBS were licensed by Corvita Corporation (Miami, FL, Acquired by BSC, Natick, MA) and strengthened by additional patents covering applications in the medical implant arena [28–30].

The triblock SIBS, was used for the initial studies of biocompatibility and biostability. Fig. 4 shows the molecular structure of SIBS in which soft PIB rubbery chains are held together by hard glassy polystyrene domains. Fig. 5 shows a cartoon of the synthesis and architecture of this thermoplastic elastomer. Dangling chains are absent and all the PIB segments contribute to the load-bearing capacity of the network. SIBS is a self-assembled physically crosslinked PIB, and thus thermo- and solution-formable. Furthermore, because it is soluble in various non-polar solvents it can be spray-coated or solvent cast to deliver soft strong coherent films.

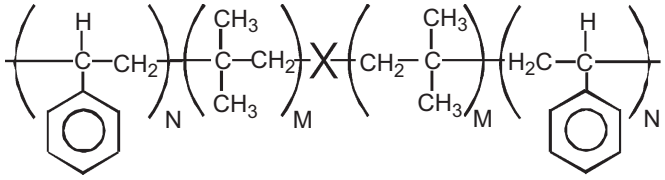

Fig. 4. Schematic of poly(styrene-*block*-isobutylene-*block*-styrene) ("SIBS"), where $N/(M+N)$ for biomedical application is generally 0.05–0.50. X is the residue of the hindered dicumyl ether initiator (see Fig. 6).

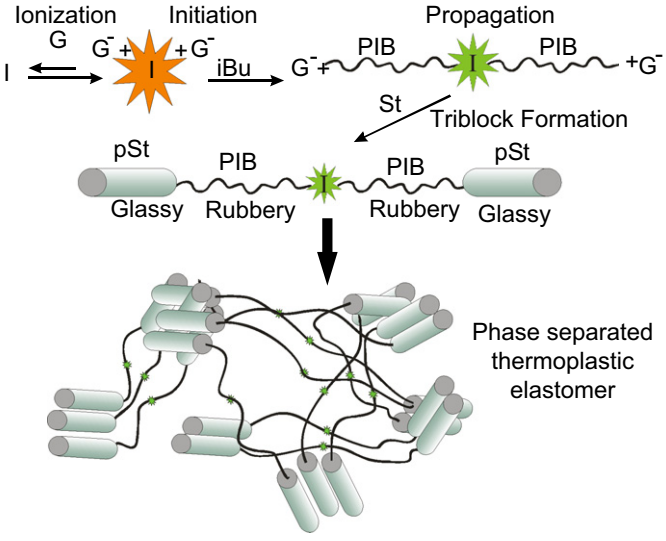

Fig. 5. Cartoon of the synthesis stages of SIBS, showing ionization, initiation, propagation and block formation.

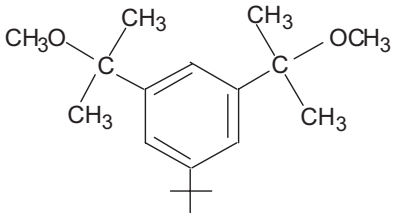

Fig. 6. 5-*Tert*-butyl-1,3-bis(1-methoxy-l-methylethyl)-benzene, also called 5-*tert*-butyl-1,3-dicumyl ether (MW 278), AKA hindered dicumyl ether (HDCE).

4. The synthesis and properties of SIBS

SIBS is synthesized by the living cationic polymerization technique developed by Kennedy's team at The University of Akron. Living cationic polymerization, a seminal discovery in polymer science, lead not only to SIBS but also to many novel compositions useful for a variety of industrial and medical applications [27].

The synthesis of SIBS begins with a bifunctional initiator, which becomes part of the polymer. The preferred initiator is 5-*tert*-butyl-1,3-bis(1-methoxy-l-methylethyl)-benzene (for brevity's sake "hindered dicumyl ether", abbreviated HDCE). HDCE is not commercially available and is custom synthesized by Innovia LLC (Miami, FL) according to methods developed by Kennedy et al. [31,32].

In brief, SIBS is prepared in two steps in one pot: First isobutylene is polymerized by a HDCE/$TiCl_4$ initiating system in a methyl chloride/hexanes solvent system in the presence of a proton trap under a blanket of dry nitrogen at −80 °C. When the central PIB block reaches the desired molecular weight, styrene is added and the polymerization is continued until the outer polystyrene blocks also reach a predetermined length. The process is terminated by the addition of methanol. Fig. 7 outlines the synthesis of SIBS.

Table 1 presents typical properties of SIBS. The molecular weight of the triblock is controlled by reaction conditions, mainly by the ratio of monomers/initiator. The hardness of SIBS can be varied by the amount of styrene employed. Fig. 8 shows a plot of Shore hardness in both the A scale and D scale as a function of mole percent polystyrene in SIBS.

The excellent oxidative stability of SIBS can be demonstrated by submerging a swatch of SIBS in boiling concentrated (65%) nitric acid for 30 min. Whereas other elastomers used for implant applications, such as silicone rubber and polycarbonate urethane, severely embrittle or are completely destroyed within a few minutes, SIBS remains relatively unscathed and stable under these harsh conditions [28]. Silicone rubber (PDMS) is well-known to degrade by strong acids and strong bases [33].

SIBS can be injection and compression molded, as well as extruded and solvent cast from non-polar solvents such as methylcyclohexane, cyclopentane, toluene and tetrahydrofuran. Furthermore, components made from SIBS can be solvent-bonded with these non-polar solvents.

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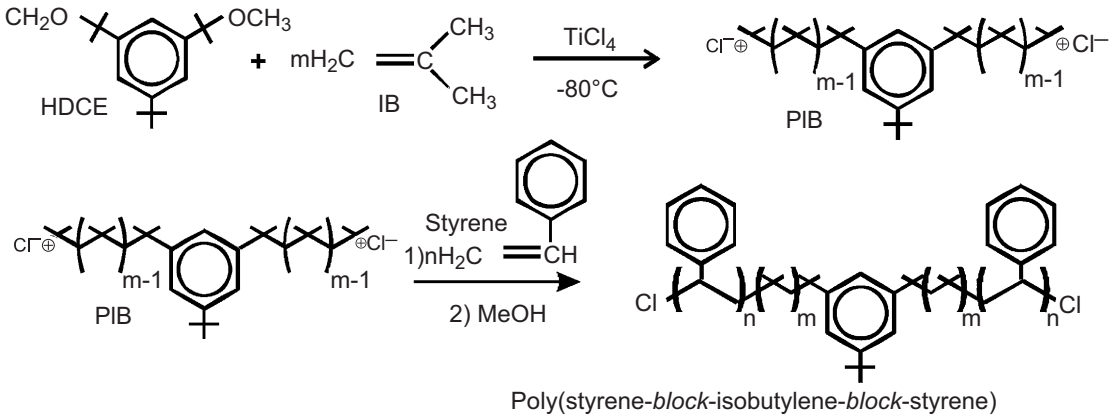

Fig. 7. Reaction scheme for the synthesis of SIBS using living cationic polymerization.

Table 1
Typical physical properties of SIBS triblock polymers

Shore hardness	30A–60D
Mole percent styrene	5–50
Ultimate tensile strength (psi)	2000–5000
Ultimate tensile strength (MPa)	10–30
Ultimate elongation (%)	300–1100
Index of refraction	1.525–1.535
Water absorption (g/m^2 at 24 h)	0.2–0.3
Weight average molecular weight	60,000–150,000
Polydispersity (Mw/Mn)	1.2–2.1

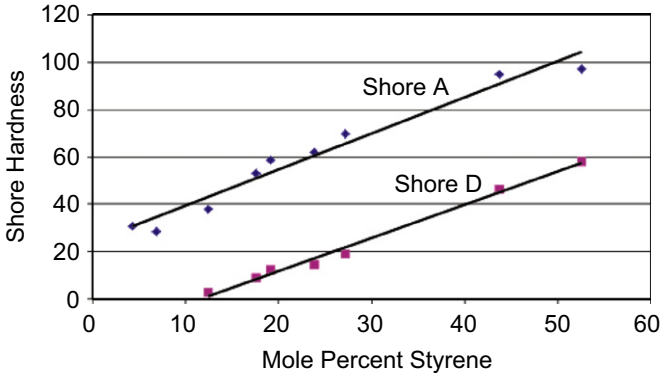

Fig. 8. Plot of mole percent styrene in SIBS versus shore hardness (courtesy of Yonghua Zhou and John B. Martin (Innovia LLC, Miami, FL)).

The downside of the thermoplastic nature of SIBS is that (1) it is susceptible to stress cracking in the presence of organic solvents; (2) it has poor creep properties and therefore requires fiber reinforcement for certain load-bearing applications (see heart valves below); (3) the non-polar nature of SIBS does not allow sites for hydrogen bonding, as in polyurethanes, which limits its ultimate tensile strength to less than that of a dry polyurethane; (4) it has poor gas permeability which renders it more cumbersome to sterilize with ethylene oxide as all surfaces must be exposed to the gas (this is in contrast to silicone rubber which is permeable to ethylene oxide); (5) SIBS is not gamma-ray sterilizable; (6) the cost of synthesis and purification of SIBS is, at the present production rate, relatively high, and; (7) due to intellectual property constraints, there is no source for implant-grade material, other than small amounts, that may or may not be available from Innovia LLC.

5. SIBS in medicine

5.1. Stent-grafts

The first two embodiments of SIBS to be tested for long-term implant were: (1) a microporous liner on a stent; i.e., as a stent-graft, and (2) approximately 1 mm diameter monofilaments. The stent-grafts were constructed by rotating a braided wire mesh stent on a mandril while spraying it with SIBS dissolved in tetrahydrofuran. The SIBS filaments were formed in mid-air as the tetrahydrofuran flashed off thereby depositing a porous tubular mat. Animal studies were initiated with a protocol that required explants of the monofilaments at 1 and 3 months, and explants of the porous stent-graft at 6, 12 and 24 months. The monofilament data demonstrated absence of biodegradation by scanning electron microscopy examination and by tensile strength measurement [34,35]. The 6, 12 and 24-month explants of the stent-graft liners showed intact structures with no fiber cracking or biodegradation by scanning electron microscopy (tensile strength data were not acquired because the liners were attached to stent

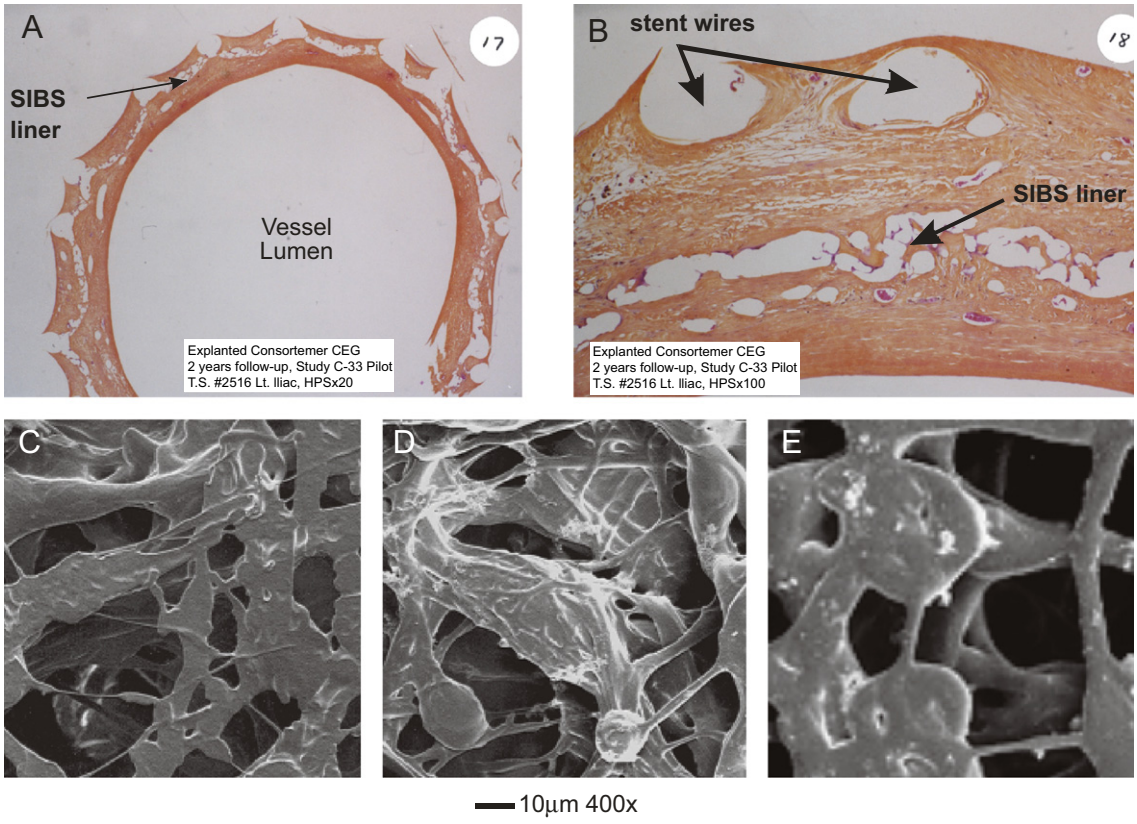

Fig. 9. (A) Cross-section of a 6 mm diameter stent-graft, made with sprayed SIBS fibers explanted after 24 months in the iliac artery of a dog (HPS stain (20 ×)). (B) The same graft as (A) at 100 × magnification showing excellent tissue ingrowth. (C) A pre-implant SEM of the sprayed SIBS microfibers. (D) and (E) are explants at 6 and 24 months, respectively, showing no fiber cracking (C–E are from Ref. [35]).

struts). Figs. 9A and B show the histology of the explanted stent-graft at 2 years demonstrating excellent tissue integration and wide patency. Figs. 9C–E show approximately 5 µm diameter fibers, before implant and at both 6 months and at 2 years explant indicating no cracking. Molecular weight constancy of these polymers was corroborated using gel permeation chromatography (GPC) of 1-year explants from coronary stents by Steckel et al. [36] from Barry's group at Boston Scientific. It is noteworthy that the SIBS coating was in intimate contact with the stainless steel stent and remained unaffected by metal ion oxidation.

It was also observed throughout the implant study by Wilson's group, as well as by Boston Scientific researchers, and in many other SIBS explants in both animals and humans, that there were usually very few, if any, PMNs around SIBS, which is in contrast to the significant accumulation of PMNs observed around implanted polyurethanes. The smaller recruitment of PMNs suggests that the biostable nature of SIBS may play a significant role in controlling the foreign body reaction.

5.2. *SIBS as the drug carrier in the TAXUS® drug-eluting coronary stent*

Boston Scientific Corporation (BSC—Natick, MA) scientists began evaluating SIBS as a drug carrier in their drug-eluting coronary stent program. BSC was actively researching the use of paclitaxel, delivered in a controlled manner from a stent to minimize the process of in stent restenosis (re-occlusion of the coronary artery after stent implantation) which occurred in approximately 35% of all patients receiving a coronary stent. Paclitaxel, at appropriate concentrations, functions by promoting the formation of stable microtubules in cells and reduces proliferation and migration of smooth muscle cells in the arterial wall. It is through these proliferative processes that the lumen of the artery can narrow. Two comprehensive reviews of paclitaxel and its mechanism of interaction with smooth muscle cells on a stent, as well as the preclinical and clinical trials of the TAXUS® drug-eluting stent, are provided by Kamath et al. [37,38] from Barry's group. The present publication briefly reviews the importance of SIBS in this drug-eluting application. Boston Scientific scientists were attempting to release paclitaxel from a polycarbonate urethane coated onto their stent. Several *in vivo* studies showed a consistent inflammatory response characterized by PMN infiltration around polyurethane-coated stent struts. Fig. 10A shows a cross-section of a 2-month explant from a porcine coronary artery implanted with a non-coated-bare-metal coronary stent (BMS) showing the expected widely patent lumen and paucity of inflammation. However, when the stent struts were coated with polycarbonate urethane, it elicited a very strong inflammatory

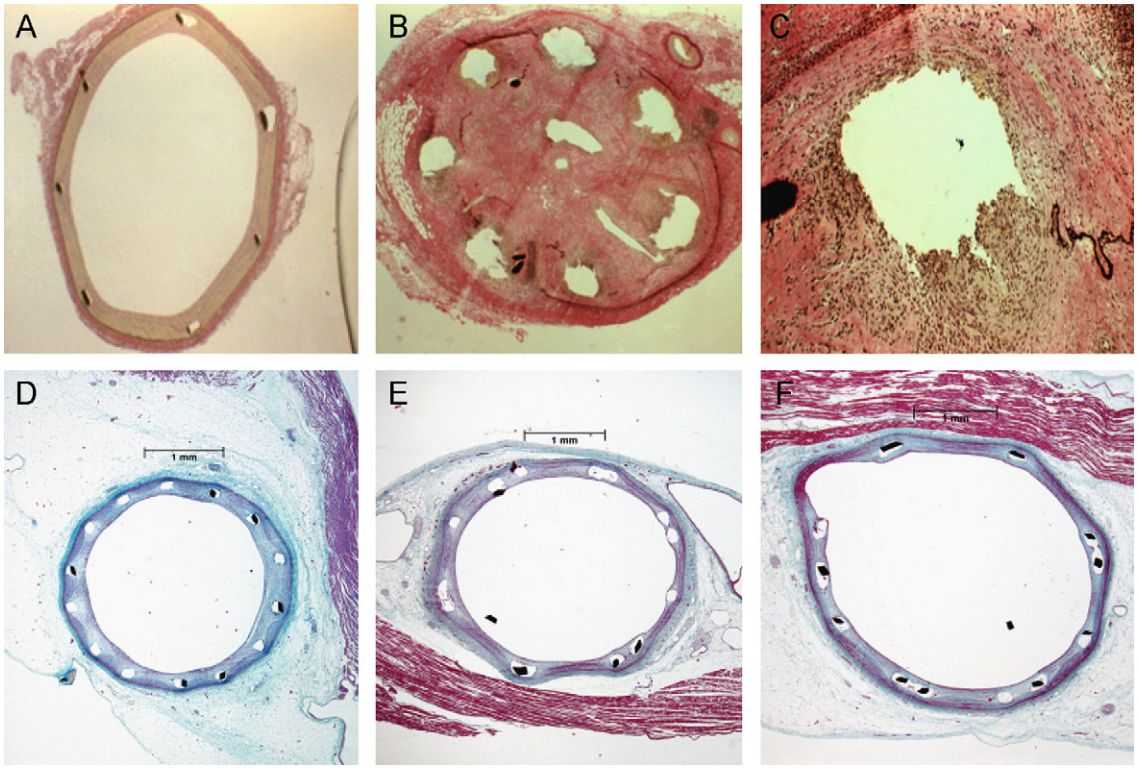

Fig. 10. Cross-section of porcine coronary arteries with stent explants at various time points: (A) BMS (non-coated stent) at 2 months; (B) a polycarbonate urethane-coated stent with significant inflammation and hyperproliferation (2 months); (C) a high magnification of B showing the presence of PMNs (2 months). (D) BMS (3 months); (E) and (F) are stents coated with SIBS (90 and 180 days, respectively), showing wide patency. (BSC in collaboration with Elazer Edelman and Campbell Rogers, MIT [polyurethane studies, Rob Schwartz, Mayo Clinic] and Greg Wilson, Hospital for Sick Children—Toronto, Ontario.)

reaction and ultimately lumen loss (Fig. 10B). Magnification of the strut area (Fig. 10C) showed significant inflammation with infiltration by PMNs and macrophages. The hyperplastic response secondary to inflammation resulted in luminal narrowing and occlusion of the artery. The aggressive cellular reaction around the polyurethane-coated coronary stent was essentially identical to that observed around the degrading polyurethane vascular grafts shown in Fig. 1. This was a surprising observation for the BSC team given the widely reported successful use of polyurethanes in numerous medical applications. For a drug-eluting stent utilizing a polymer carrier to be successful, a highly desirable characteristic is that the polymer should not elicit a biological response worse than that of the BMS. BSC researchers subsequently began evaluating SIBS as a means of minimizing the inflammatory reaction.

SIBS was tested on a coronary stent in the porcine coronary model and it was confirmed that SIBS demonstrated a biological response similar to the BMS. Figs. 10D–F show a BMS stent following 90 days implantation as well as a SIBS-coated stent at 90 and 180 days post-operatively, respectively. These experiments clearly showed that patency in these 3 mm diameter coronary arteries could be maintained with SIBS-coated stents. In addition Kamath reported that SIBS-coated stents showed platelet adhesion and activation at a level comparable to that of the BMS in the absence and presence of paclitaxel, and this observation held true for periods greater than 1 year in their challenging porcine coronary model. Further testing by Barry's group with stents coated with SIBS/paclitaxel combinations revealed, after a few dosing iterations, that paclitaxel released in a controlled manner from SIBS could mitigate the restenosis of coronary arteries in animals [37–42]. Extensive clinical trials have confirmed these same findings in humans [43].

Fig. 11 shows an atomic force micrograph (AFM) as well as a transmission electron micrograph (TEM) of SIBS/paclitaxel coated on a coronary stent. Although paclitaxel is lipophilic, it is insoluble in the hydrophobic SIBS and tends to disperse into small islands within the polymer matrix. Accordingly, after an initial burst from the surface following implantation, most of the paclitaxel remains in the polymer. Work on blends of SIBS with other polymers, such as poly(styrene-*r*-maleic anhydride) [44] and poly(-alkyl methacrylate-*b*-isobutylene-*b*-alkyl methacrylate) [45] are ongoing to improve control of the release kinetics of paclitaxel as well as other drugs from the bulk of the drug carrier. Initial clinical trials of the TAXUS® stent were conducted by Grube and Bullesfeld [46] (Heart-Center Siegburg, Germany) who reported on BSC's TAXUS-I safety trial (paclitaxel/SIBS-coated NIR stent (Tel Aviv, Israel)). At 6 months follow-up, there were 0% restenosis in the TAXUS arm versus 10% in the BMS control group.

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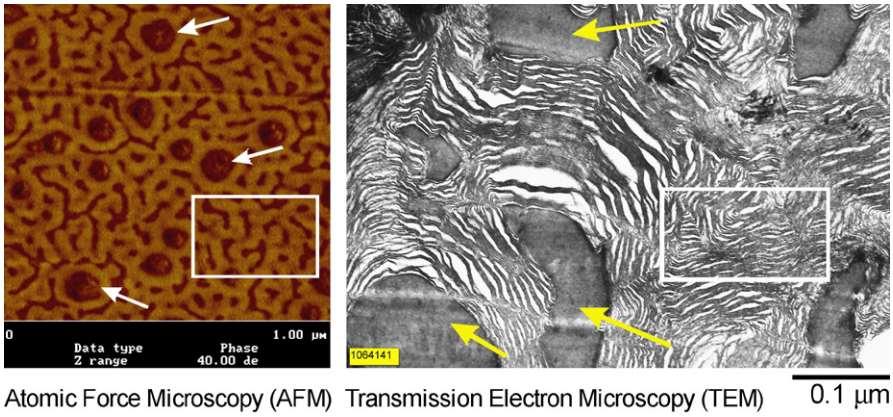

Fig. 11. AFM and TEM of SIBS showing islands of 8.8% w/w paclitaxel (see arrows) that are insoluble in the SIBS matrix (white rectangles) (Courtesy of Ranade et al., from BSC).

In addition, there were no incidences of thrombotic events. These studies combined with the TAXUS II study [47] helped support filings with the United States Food and Drug Administration resulting in the ultimate release of the TAXUS® Stent to the US market.

Several other studies of the TAXUS® Stent were published following its initial launch and are summarized in Kamath's review articles [37,38]. The TAXUS® Stent continues to demonstrate the beneficial long-term durability and efficacy of a drug-eluting stent in preventing restenosis as well as its safety out to 4 years follow-up from the time of this writing [43]. It is important to recognize that other groups have attempted to place paclitaxel on a stent with limited success in reducing restenosis [48,49]. This exemplifies the importance of the polymer carrier, in this case SIBS, as a critical component for the success of drug-eluting stents for treating coronary artery disease.

More recently, it has been reported that all drug-eluting stents available in the US are indicating a slight increase in late stent thrombosis that appears to be primarily attributed to patients prematurely discontinuing their systemic anti-coagulation therapy [50]. However, a recent FDA sponsored expert panel on this topic overwhelmingly supported the benefits of drug-eluting stents over the risk of late stent thrombosis in patients who are indicated for a drug-eluting stent [51].

The drug-eluting stent is the most recent treatment of coronary artery disease over the last 30 years. In a field that evolved from coronary bypass surgery, to balloon angioplasty with up to 60% restenosis rates, to bare-metal stents with up to 40% restenosis, to the drug-eluting stent—this technology offers a significant improvement of quality of life for hundreds of thousands of patients.

5.3. SIBS in ophthalmology: the MIDI-Tube glaucoma shunt

Work performed by Parel and his colleagues (The University of Miami's, Miller School of Medicine, Bascom Palmer Eye Institute, Miami FL) in conjunction with scientists at InnFocus LLC (an Innovia spin-off, Miami, FL), showed that SIBS disks implanted in the stroma of the cornea (Fig. 12), and in the sub-Tenon space in the eye, are significantly less irritating and inflammatory than similarly shaped PDMS controls [52,53]. It was discovered during this first set of implants in rabbits that SIBS barely encapsulates in the eye as compared to PDMS, which demonstrates significant encapsulation and concomitant angiogenesis. The first application leveraging this finding was a glaucoma drainage tube, called the "MIDI-Tube", first described by Acosta et al. [54] from Parel's group. The MIDI-Tube, illustrated in Fig. 12, is an 11 mm long, 250 µm diameter SIBS microtube with a small tab (fin) located half-way along the length of the tube to prevent migration of the tube into the anterior chamber.

The lumen of the tube, determined by the Hagen-Poiseuille equation [55], is between 60 and 100 µm in diameter to prevent hypotony (deflation of the eye with subsequent collapse of the anterior chamber) without the need for an intrinsic pressure relief valve. The tube is introduced into the anterior chamber from a needle tract located 2 mm posterior to the limbus that is tunneled under the limbus and exits in the anterior chamber. As illustrated in Fig. 12, the proximal end of the MIDI bisects the angle between the iris and the cornea with the tip of the tube located 2 mm into the anterior chamber. The distal end of the tube rests in a subconjunctival/Tenon flap created posterior to the limbus, extending to the equator of the eye. A shallow bleb (a blister-like structure) forms in the conjunctival flap as aqueous humor drains from the anterior chamber. Fluid from the bleb is absorbed into the venous system of the eye or through the conjunctiva into the tear ducts, depending upon the health of the tissue surrounding the device. This shunting of fluid from the high-pressure interior of the eye to the near atmospheric pressure of the bleb, effectively lowers the pressure in the eye.

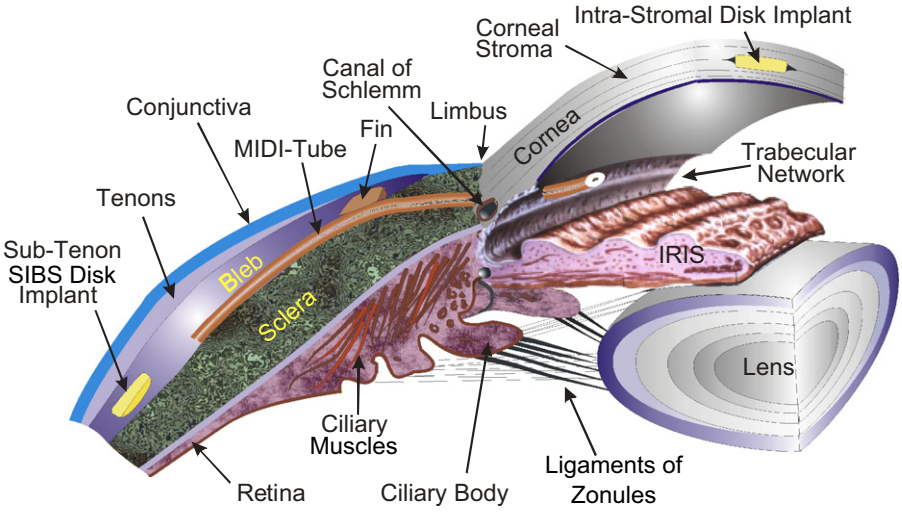

Fig. 12. Schematic of the eye showing the sites for the intrastromal SIBS disk implant and the sub-Tenon SIBS disk implant. Also shown is the MIDI-Tube, which conducts aqueous humor from the anterior chamber to a bleb formed under the conjunctiva/Tenons as a means of reducing pressure in the eye to treat glaucoma.

The MIDI-Tube was tested in 41 New Zealand White Rabbits; 22 with a 70 μm, 6 with a 100 μm and 4 with a 150 μm lumen diameter tube and 9 with PDMS tube controls (OD, 600 μm; ID, 300 μm; length, 19 mm). Follow-up at various intervals up to 14 months showed no inflammation, migration or extrusion of the MIDI-Tube. Flow patency in the SIBS group was confirmed in all cases by fluorescein (0.01% in saline) injection into the anterior chamber with subsequent drainage through the tube into the bleb. There were no incidences of hypotony or flat chambers at post-operative day 1. Slit-lamp and optical coherence tomography (OCT) exams showed clearance of the proximal entrance and no clogging along the tube, a normal anterior chamber and a quiet ocular surface. Light microscopy and immunostaining against collagen IV, macrophages and α-smooth muscle actin demonstrated a distinct absence of myofibroblasts and inflammatory cells with minimal scarring in the MIDI group. In contrast, the silicone rubber tubes demonstrated patency in only 2/9 devices at 6 months and immunostaining showed myofibroblasts and significant capsular formation. An independent 6-month biocompatibility study of the MIDI-Tube (without PDMS controls), performed at NAMSA (North American Science Associates, Inc., Toledo, OH) in 10 rabbits using good laboratory practices (GLPs), yielded similar results with SIBS tubes, showing only one migration of a device due to an iatrogenically damaged tab [52,56–58].

It is interesting to speculate why silicone rubber leads to significant encapsulation in both the initial disk implants and in the glaucoma tube studies within the subconjunctiva of eye, whereas SIBS does not, keeping in mind that tissue interfaces methyl groups in both polymers. PDMS, which is synthesized by ring opening polymerization of octamethylcyclotetrasiloxane, may elute unreacted cyclics into adjacent tissue and may attract PMNs. In addition, silicone rubber is unstable at both high and low pH [33], and acids produced by PMNs, macrophages and the like may cleave moieties which may be chemotactic towards additional phagocytes. In contrast, SIBS is stable at extreme pH ranges.

SIBS has also been used successfully as a scleral buckle in rabbits for the possible reattachment of detached retinas [59]. The advantage of SIBS for this application is that SIBS does not significantly encapsulate and is therefore thinner with less chance of restricting eye motion. Furthermore, it is removable as compared to silicone rubber, which tends to form large capsules and remain in the patient for life.

SIBS is also a candidate for use as an intraocular lens (IOL) or anterior chamber lens as it has a high refractive index of 1.525–1.535 at all hardnesses. In addition, it does not have a yield point at durometers less than Shore 50A and can be folded or rolled without scratching or surface cracking and therefore can be introduced into the lens capsule through a cannula less than 2 mm in diameter. Further, due to the high flex fatigue life of SIBS (see heart valve section), it may be of use as an accommodating IOL to treat presbyopia. Accommodating IOLs may enable post-cataract patients to see both far and near without wearing spectacles. Lenses, both with and without haptics, have been cryogenically machined from SIBS and there is no reason why such lenses could not be injection or compression molded. Pilot implantations of two IOLs in two rabbits at the Bascom Palmer Eye Institute's Ophthalmic Biophysics Center, by Viviana Fernandez, showed excellent biocompatibility. What remains to be seen is whether the creep behavior of SIBS will force it to take an undesirable shape in the lens sac. Lastly, it has been hypothesized that the lack of cleavable side groups from SIBS may provide a lens with less chronic corneal endothelial damage as compared to

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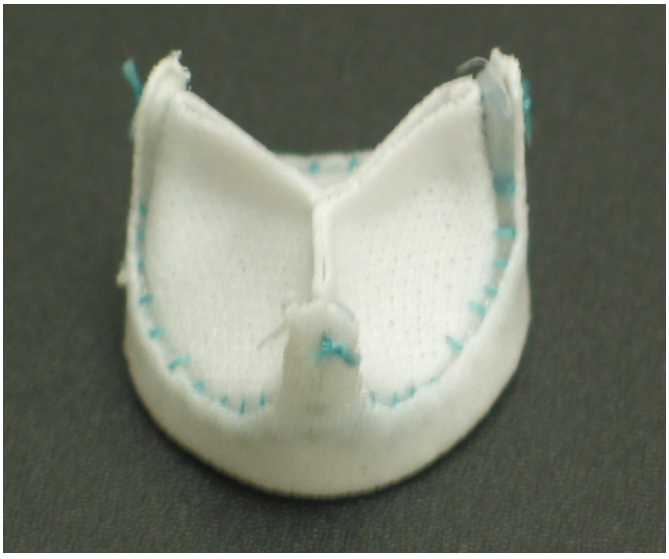

Fig. 13. The all-synthetic flow-through heart leaflet valve for replacement of the aortic valve. The leaflets are comprised of a composite of PET and SIBS. The valve stent is of a harder durometer SIBS (courtesy of Siobhain Lowe, Florida International University).

conventional lenses that show continual loss of endothelial cells with time [60]. This hypothesis has yet to be substantiated.

5.4. SIBS for a synthetic trileaflet aortic valve

Schoephoerster's group at Florida International University (Miami, FL) demonstrated that SIBS has a high flex fatigue life and when reinforced with PET fibers or fabric, exhibits minimal creep deformation. Unreinforced SIBS, like most other thermoplastics, will creep. Creep resistance, combined with excellent hemocompatibility and biostability, suggests that SIBS may be suitable for use in a through-flow heart leaflet valve [61–66]. A composite heart valve leaflet has been designed (Fig. 13) with low modulus SIBS (7–9 mol% styrene), reinforced with a knitted polyester fabric, and attached to a SIBS frame of significantly higher modulus (35–40 mol% styrene). Animal implants and long-term *in vitro* flex fatigue studies are ongoing (fatigue lives are currently in excess of 400 million cycles, which approximates 10 years of operation in a human). It is anticipated that the inertness of SIBS will prevent degradation and intrinsic calcification which has been the bane of other polymers, especially polyurethane, which have been tested extensively for this application.

6. Conclusions and future work

SIBS is a biostable thermoplastic elastomer with properties ideal for certain medical implant applications. Initial data collected with SIBS liners on stent-grafts and coatings on stents demonstrate hemocompatibility, biocompatibility and long-term stability in contact with metal. SIBS has been used successfully in drug-eluting coronary stents and its uses are being investigated for ophthalmic implants, synthetic heart valves and other applications. At the present, researchers developing medical devices utilizing SIBS have found the following: (1) SIBS does not substantially activate platelets in the vascular system; (2) PMNs in large numbers are not commonly observed around SIBS implants in the vascular system or in subcutaneous implants or in the eye; (3) myofibroblasts, scarring and encapsulation are not clinically significant with SIBS implanted in the eye; (4) embrittlement has not been observed in any implant location; (5) calcification within the polymer has not been observed; (6) degradation has not been observed in any living system to date; (7) creep deformation needs to be addressed in certain load-bearing applications; and (8), care must be taken when sterilizing SIBS with ethylene oxide to ensure all surfaces are well-exposed to the gas. The reason for the excellent biocompatibility of SIBS may be due to the inertness of SIBS and lack of cleavable moieties that could be chemotactic towards inflammatory cells. This inertness distinguishes SIBS from other implantable polymers such as the acrylates, methacrylates, polyesters, polyethers, polyamides and polyurethanes that contain ester, ether, amide or carbamate groups, which may slowly hydrolyze, oxidize or cleave side groups which may be chemotactic towards phagocytes. An abundance of these scavenger cells can lead to thick capsules and/or other undesirable sequelae.

PIB-based polymers are continuously evolving. Kennedy's and Puskas's groups at The University of Akron; Faust's laboratory at the University of Massachusetts (Lowell, MA); Innovia and its Affiliates and BSC are working on advanced chemistries that include injectable polymers that polymerize in the body, as well as hydrophilic and enhanced hydrophobic designs for controlled drug delivery. In addition, tougher, and more lubricious materials are being developed for orthopedic and spinal applications to replace the failing polyethylenes [23] and polyurethanes [1] which are prone to oxidation by body fluids. It is anticipated that PIB-based polymers will play a major role in many new medical devices in the future.

Acknowledgments

The six co-authors of this review are the team leaders from multiple academic institutions and commercial entities who have been responsible for bringing SIBS research and medical product development to its present state. The six teams collectively comprise many engineers, chemists, materials scientists, physicians and academic trainees to whom we are grateful. In regard specifically to manuscript preparation, the authors wish to thank Marcia Orozco for her help in organizing this manuscript, Yonghua Zhou and John Martin for providing the data on percent styrene versus hardness of SIBS and Kalpana Kalmath for help in TAXUS® research.

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