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Review

Medical applications of poly-4-hydroxybutyrate: a strong flexible absorbable biomaterial

David P. Martin*, Simon F. Williams

Tepha Inc., 303 Third Street, Cambridge, MA 02142, USA

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Abstract

Poly-4-hydroxybutyrate (P4HB) is being developed as a new absorbable material for implantable medical applications. P4HB promises to open up new opportunities for the development of medical applications by offering a new set of properties that are not currently available. The absorbable biomaterial is strong yet flexible, and degrades in vivo at least in part by a surface erosion process. While the chemical structure of P4HB is similar to that of current absorbable polyesters used in implantable medical products, P4HB is produced by a fermentation process rather than through a chemical synthesis. P4HB is a thermoplastic material that can be processed using standard plastics processing techniques, such as solution casting or melt extrusion. The strength of P4HB fibers prepared by melt extrusion compare well with that of traditional suturing materials, however, P4HB is typically more flexible. P4HB should find use in a wide variety of medical fields such as cardiovascular, wound healing, orthopedic, drug delivery, and tissue engineering applications. This paper describes some of the basic properties of P4HB and several of its potential applications in medicine.

Keywords: Poly-4-hydroxybutyrate; Biomaterial; Fermentation; Absorbable; P4HB

1. Introduction

Poly-4-hydroxybutyrate (P4HB) is a polyester that is currently being developed as a new absorbable biomaterial for medical applications. The biomaterial offers a new set of properties that significantly extends the existing biomaterial design space allowing the development of new and improved products. In the field of cardiovascular research, for example, the use of P4HB has resulted in the first successful demonstration of a tissue engineered tri-leaflet heart valve in a sheep model. Other products under development include vascular grafts, stents, patches, and sutures. This review describes some of the progress in the development of this new biomedical polymer, its properties, uses and potential applications in medicine.

2. Preparation and properties

In contrast to other absorbable polyesters currently used in medical applications, P4HB is produced through a fermentation process, rather than a chemical synthesis. The polyester is a homopolymer of 4-hydroxybutyrate (4HB), and belongs to a diverse class of materials called polyhydroxyalkanoates (PHAs) that are derived from microorganisms (for reviews on PHAs, see [1] and [6]). In nature, these polyesters are produced inside cells as storage granules and regulate energy metabolism, but they are also of great commercial interest because of their unique properties and relative ease of production. Despite the method of preparation, the structure of P4HB (see Fig. 1) strongly resembles that of chemically derived polyesters. However, because it is biologically produced it does not contain residual metal catalysts that are used in the chemical synthesis of other polyesters. Some biosynthetic pathways that are known to produce P4HB are shown in Fig. 2 [2,3].

The chemical synthesis of P4HB has been attempted, however, it is generally considered impossible to produce the polyester by this method with sufficiently high molecular weight necessary for most applications [4]. Typically, chemical synthesis by ring-opening polymerization of γ-butyrolactone (GBL) produces only low molecular weight oligomers that are viscous fluids rather than the much higher molecular weight, strong and flexible plastic that is derived from the fermentation process.

* Corresponding author. Tel.: +1-617-492-0505; fax: +1-617-492-1996.
E-mail address: martin@tepha.com (D.P. Martin).

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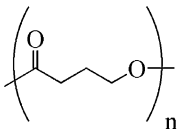

Fig. 1. Chemical structure of poly-4-hydroxybutyrate (P4HB).

2.1. Production

Tepha Inc. (Cambridge, MA) currently produces P4HB (known commercially as PHA4400) for medical applications using a proprietary transgenic fermentation process that has been specifically engineered to produce this homopolymer. During the fermentation process, P4HB accumulates inside the fermented cells as distinct granules. The polymer can be extracted in a highly pure form from the cells at the end of the fermentation process.

The heart of the process is a genetically engineered *Escherichia coli* K12 microorganism incorporating new biosynthetic pathways to produce P4HB. Using *E. coli* K12 has several advantages. First, this microorganism is the workhorse of the biopharmaceutical industry, is well understood, and used widely to produce products for human use. (Other microorganisms that could be engineered for P4HB production are not as well characterized for medical use.) Second, native *E. coli* K12 cannot produce these biosynthetic polyesters so there is no contaminating background activity, and third, this microorganism is highly efficient. Typically, yields of P4HB exceed 50 g per liter of fermentation broth in less than 48 h making large-scale production attractive.

The fermentation approach has some additional advantages. For example, it opens up additional options for tailoring properties by incorporating other co-monomers, and for varying molecular weight. To this end it is currently known that microorganisms can incorporate over 100 different types of hydroxy acids into polyesters [5]. Polymerization of 4HB with other hydroxy acids such as 3-hydroxybutyrate (3HB), for example, can yield elastomeric compositions at moderate 4HB contents (20–35%), and relatively hard rigid polyesters at lower 4HB contents [6]. Moreover, since molecular weight depends upon the activity of specific pathway enzymes within the cells, and these activities can be varied, there is a means to control molecular weight [7]. P4HB molecular weights up to about 1 million have been produced with a polydispersity of 2–3.

Although further details of the commercial P4HB production process have not been reported, the United States Food and Drug Administration (FDA) has issued a Device Master File Number to Tepha for this biomaterial. The file includes information on the production system, process, and biocompatibility of P4HB, and provides a basis for development of medical products with this new material.

2.2. Mechanical properties

P4HB may generally be described as a strong pliable thermoplastic material, and in this respect it is significantly more flexible (by up to two orders of magnitude) than synthetic absorbable polymers such as polyglycolide (PGA) and poly-L-lactide (PLLA) as shown in Table 1. Relative to other thermoplastics, P4HB has a tensile strength that benchmarks closely to ultrahigh molecular weight polyethylene. Its elongation to break at around 1000%—which means that it can be stretched 10 times its original length before breaking—is truly remarkable.

As stated above, copolymerization of 4HB with other hydroxy acids can further extend the range of properties available to include absorbable elastomeric compositions with a range of durometer hardness (see Table 2). For example, random copolymers of 4HB and 3HB are elastomeric at approximately 20–35% 4HB content providing materials that extend and return with force. These novel elastomers are currently under development for use in absorbable medical devices.

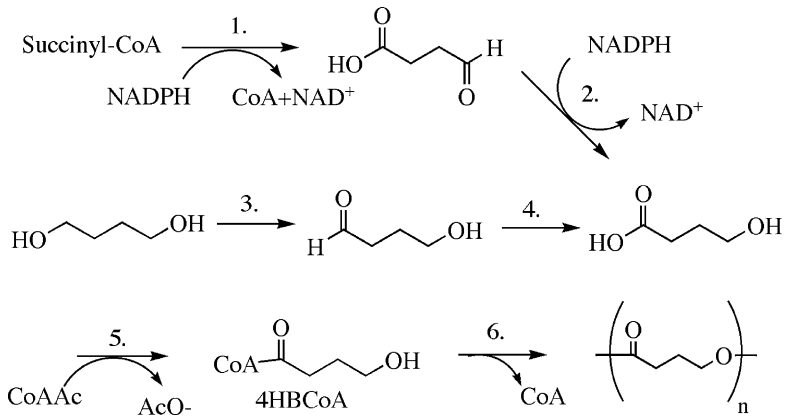

Fig. 2. Biosynthetic pathways for the production of P4HB. Pathway enzymes are: (1) succinic semialdehyde dehydrogenase; (2) 4-hydroxybutyrate dehydrogenase; (3) diol oxidoreductase; (4) aldehyde dehydrogenase; (5) coenzyme A transferase; and (6) PHA synthetase.

Table 1
Comparison of properties of P4HB with other absorbable thermoplastic polyesters

	T_m (°C)	T_g (°C)	Tensile strength (MPa)	Tensile modulus (MPa)	Elongation at break (%)	Absorption rate
PGA	225	35	70	6900	<3	6 weeks
PLLA	175	65	28–50	1200–2700	6	1.5–5 years
DL-PLA	Amorphous	50–53	29–35	1900–2400	6	3 months
P3HB	180	1	36	2500	3	2 years
PCL	57	−62	16	400	80	2 years
P4HB	60	−51	50	70	1000	8–52 weeks

Comparative mechanical data is taken from [8]. Abbreviations are: DL-PLA, copolymer of D- and L-lactide; P3HB, poly-3-hydroxybutyrate; PCL, polycaprolactone.

2.3. Processing

A wide range of options is available for processing P4HB. As shown in Table 1, P4HB has a melting temperature (T_m) of 60 °C, and glass transition temperature (T_g) of −51 °C. It is fairly stable in the melt up to about 200 °C, showing only modest molecular mass loss. As such, P4HB has a broad thermal processing window. High molecular weight P4HB (>800 K) may require higher temperatures for processing due to its high melt viscosity. However, lower molecular mass P4HB can be melt processed fairly easily.

Unlike existing synthetic absorbable polyesters such as PGA and PLLA where poor solubility often requires the use of chlorinated solvents, P4HB is fairly soluble in solvents such as acetone and other similar polar alternatives. This is particularly useful in solution coating, phase separation techniques to make porous devices, and preparation of microspheres, and could facilitate solution-spinning methods.

P4HB appears to be much less sensitive to hydrolysis by atmospheric or residual moisture than synthetic absorbable polyesters derived from α-hydroxy acids. While minimizing moisture will be important during processing of P4HB, rigorous drying or exclusion of moisture may not be necessary. Packaging requirements may also be reduced as the molded parts are expected to have better shelf stability than the more hydrolytically unstable poly-α-hydroxy acid materials.

2.4. Sterilization

Sterilization of P4HB is routinely performed using ethylene oxide, and has not been observed to cause any significant change to the polyester. If the polyester has been fabricated ready for use, sterilization is normally performed with a cold cycle due to the low melting temperature of the biomaterial.

Table 2
Properties of absorbable elastomeric P4HB copolymers incorporating 3HB

Percentage of 4HB monomer (by ^{1}H NMR)	Durometer hardness (Shore A scale)	Glass transition temperature, T_g (°C)
24	92.5	−10.3
28	82.3	−11.1
31	69.4	−13.2
33	62.2	−14.4
35	59.5	−17.2

In addition to the use of cold ethylene oxide, sterilization by γ-irradiation at 25–50 kGy may be possible. As might be anticipated, loss of molecular weight and increased polydispersity is observed under these conditions becoming more pronounced as the irradiation dose is increased.

3. Tissue response

3.1. Biocompatibility

There is now a large body of data indicating that P4HB is not only biocompatible but also actually often extremely well tolerated in vivo. This is perhaps not entirely surprising since hydrolysis of P4HB yields 4HB, a natural human metabolite present in the brain, heart, lung, liver, kidney, and muscle [9]. This metabolite has a half-life of just 35 min, and is thus rapidly eliminated from the body (via the Krebs cycle) primarily as expired carbon dioxide [10]. Furthermore, owing to its lower pK_a and tendency to lactonize, 4HB is less acidic than the α-hydroxy acids such as glycolic and lactic acids that are released from PGA and PLLA implants. The pharmacology of 4HB is well understood, and the FDA has in fact recently approved the administration of very large doses of this metabolite for the treatment of cataplexy attacks in patients with narcolepsy. Notably, multi-gram doses of 4HB monomer with repeat doses every 2–4 h are required to induce these effects. Small P4HB implants on the other hand are not expected to induce these pharmacological effects particularly in view of the relatively slow rate of conversion of P4HB to 4HB and its rapid metabolism.

P4HB has been evaluated by Tepha in a battery of biocompatibility tests recommended in 1995 by the Office of Device Evaluation in their general program memorandum #G95-1 “Biological Evaluation of Medical Devices” including cytotoxicity, sensitization, irritation and intracutaneous reactivity, hemocompatibility, endotoxin, and implantation. Notably, Tepha’s P4HB meets the standards set by the FDA for endotoxin with a content not exceeding 20 US Pharmacopeia (USP) endotoxin units per device even though the polyester is produced by a gram-negative microorganism that contains endotoxin as an integral component of the outer

cell surface. (High levels of endotoxin can induce fever in humans.)

3.2. Absorption

From initial studies it appears that P4HB degrades more slowly than PGA, but faster than PLLA, polycaprolactone (PCL) and other polyhydroxyalkanoates like poly-3-hydroxybutyrate (P3HB) in a subcutaneous environment (see Table 1). In one implantation study, it has been reported that the loss of mass from a P4HB implant varies with porosity [11]. When solid, 50 and 80% porous samples were implanted subcutaneously in rats, the average molecular weight of the polymer decreased significantly but independently of sample configuration. However, these samples lost 20, 50, and almost 100% of their mass, respectively, over a 10-week period, suggesting that degradation of P4HB in vivo depends in part on surface area. Furthermore, it follows that implants of P4HB are likely to undergo gradual changes in mechanical properties rather than the more abrupt changes observed with other synthetic absorbable polymers (e.g. PGA). This could potentially be advantageous in applications where a sudden loss of a mechanical property is not desirable, and a steadier loss of implant mass with concomitant growth of new tissue is beneficial. It also means that large amounts of acidic degradation products are not suddenly released from P4HB as has been observed with implants of α-hydroxy polyesters such as PGA [12].

As discussed below, more rapid degradation of P4HB has also been observed when the polyester has been used as a coating on PGA mesh. This composite was utilized as a tissue engineering heart valve scaffold in a sheep model [13] and complete absorption of P4HB was noted 6–8 weeks after implantation.

4. Applications

4.1. Congenital cardiovascular defects—artery augmentation

Each year about 40,000 babies are born in the United States with congenital cardiovascular defects [14]. These are currently the most fatal kind of birth defect, and half of these deaths occur in infants under one year of age. In all there are currently more than 1 million Americans with some form of congenital cardiovascular defect.

Cardiovascular surgeons can frequently repair these defects surgically, often with the use of a surgical patching material. In many cases, it would be advantageous to use living tissue or a tissue scaffold as a surgical patching material rather than the non-viable, synthetic materials that are often used, such as polytetrafluoroethylene (PTFE). In one such study, P4HB has been used with good success as a scaffold for preparing autologous cardiovascular tissue. Patches of P4HB with a porosity exceeding 95% and pore sizes of 180–240 μm, were prepared through a combination of salt-leaching and solvent evaporation (see Fig. 3). These scaffolds were seeded with autologous endothelial, smooth muscle, and fibroblast cells prior to being implanted to augment the pulmonary artery in a sheep model [11]. Six cell-seeded patches and one unseeded control were used in the 24-week study. At 4, 7, and 24 weeks, echocardiography and examination of the cell-seeded explants revealed progressive tissue regeneration with no evidence of thrombus, stenosis or dilation (see Fig. 4). In comparison a slight bulging and somewhat less tissue regeneration were noted at 20 weeks for the control patch. The results (which received the Medtronic Hancock Award at the 2001 meeting of the German Society of Thoracic and Cardiovascular Surgery) demonstrate the feasibility of developing a P4HB tissue scaffold for use as a cardiovascular patching material.

An additional feature of the P4HB patching material was noted by the surgeons during the course of this study that relates to its ease of use relative to conventional permanent implant materials such as PTFE. Upon implantation of the P4HB patch no bleeding was observed along the suture line, whereas bleeding is often observed after suturing of PTFE patches. Comparison of SEM images showing the results after sutures have passed through each of these materials is shown in Fig. 5. Notably, the suture leaves a hole for blood to leak through in the PTFE patch, while the P4HB patch is self-sealing preventing blood leakage. This feature of the P4HB patch may have broader application.

4.2. Heart valves

Some of the most astonishing results in heart valve development have been obtained with PHA polymers [15,16], and most recently with P4HB [13]. Heart valve replacement surgery is fairly common and the American Heart Association has estimated that more than 90,000 of these procedures are performed each year [14]. Current valves could be substantially improved, however, and this need is particularly acute for the pediatric population. Since existing heart valve prostheses are non-viable, young patients often outgrow replacement valves and need repeat surgeries to replace them. Significant improvements are also needed for the adult population to improve valve durability and reduce the need for anticoagulant therapy. A promising approach that would address all these current deficiencies is to develop a tissue engineered heart valve.

In early studies to create a tissue engineered heart valve, a group at Children's Hospital in Boston evaluated several synthetic absorbable polyesters as potential scaffolding materials for heart valves. The tissue scaffolds were seeded with cells, grown in vitro, and then implanted in the pulmonary circulation in a sheep model. Unfortunately, the success of these studies was limited as the synthetic polyesters proved to be too stiff to function as flexible leaflets inside a tri-leaflet valve [19]. In the late 1990s the same general approach was attempted, however a much more flexible material

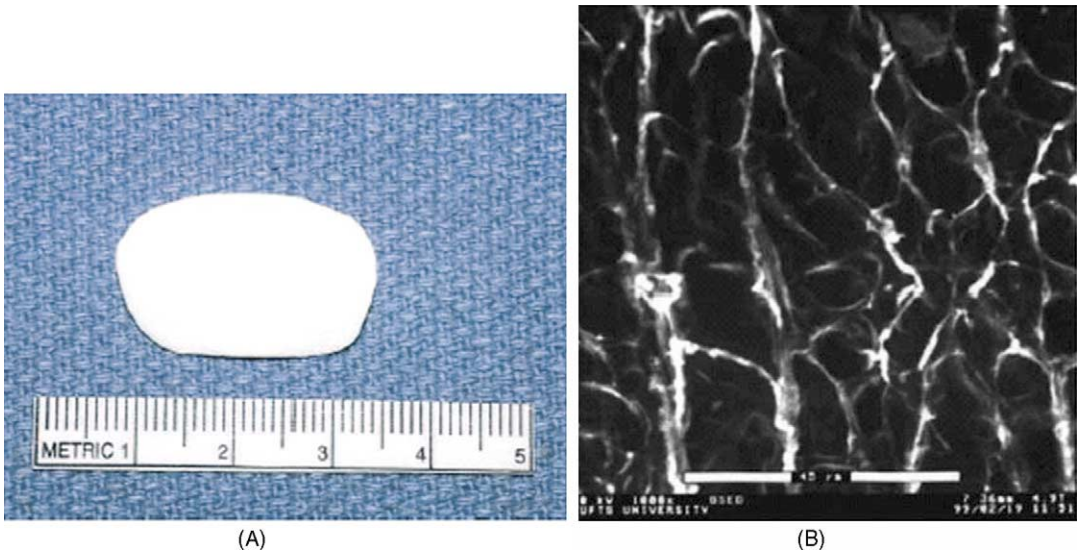

Fig. 3. Porous P4HB construct for augmentation of pulmonary artery: (A) implantable porous patch; (B) SEM of patch. Reproduced with permission from [11].

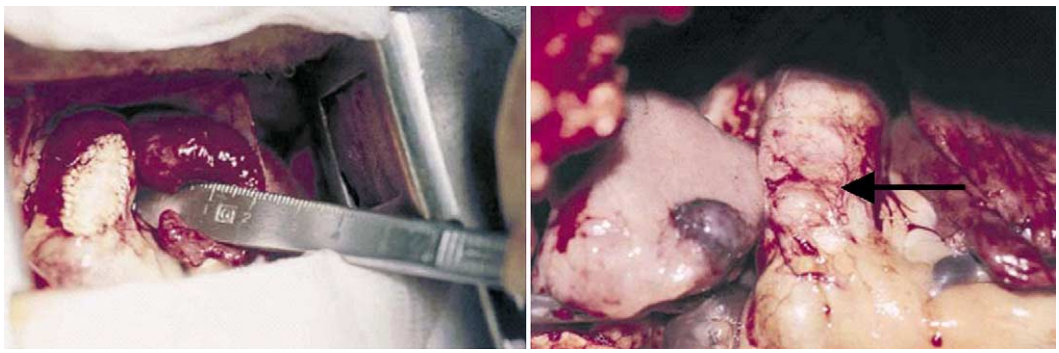

Fig. 4. Artery augmentation with a porous P4HB patch. (Left) Implanted tissue engineered patch. (Right) Patch has been replaced with new vessel tissue. Arrow shows approximate location of original implant. Reproduced with permission from [11].

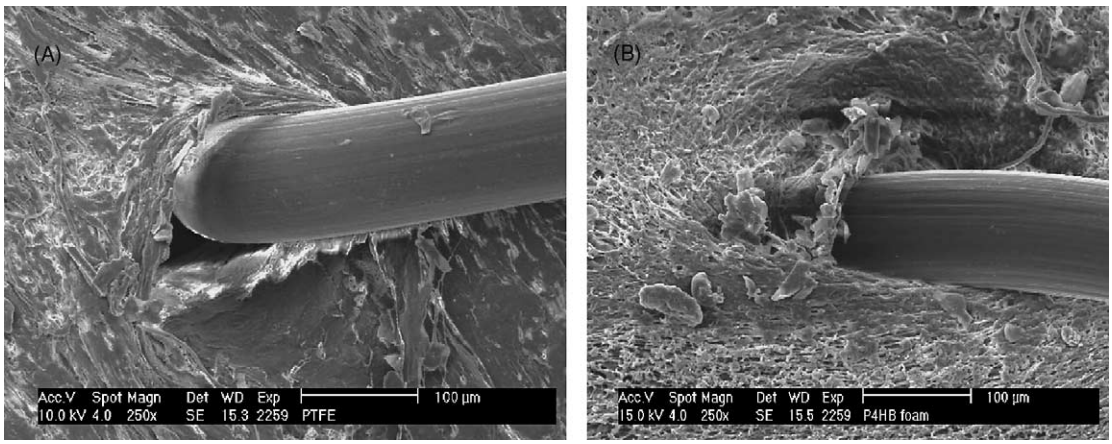

Fig. 5. SEM Images of 6/0 prolene suture passed through an ePTFE patch (A) and a P4HB patch (B). Note pin-hole in ePTFE patch on left allowing blood leakage. Reprinted with permission from Dr. Ulrich Stock.

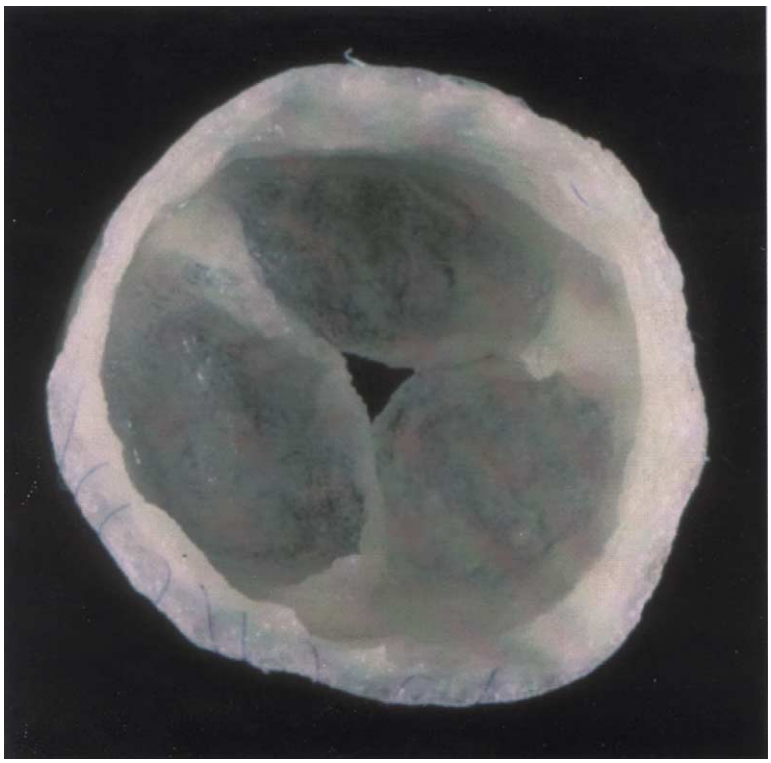

Fig. 6. Tissue engineered heart valve construct derived after in vitro tissue culture using a P4HB/PGA composite scaffold. Reproduced with permission from [13].

called poly-3-hydroxyoctanoate-co-3-hydroxyhexanoate (PHO) was used as the scaffold material for the valve leaflet [15], and subsequently the entire heart valve [16]. The results were remarkable. When the tissue engineered heart valves were implanted in the pulmonary circulation, the sheep survived the complete duration of the study, and the scaffolds began to remodel in vivo to resemble the native valve. In order to achieve more rapid tissue remodeling in vivo, the same group at Children's Hospital in Boston evaluated in subsequent studies the use of P4HB as a faster degrading alternative scaffold material [13]. A porous scaffolding material in the form of a tri-leaflet heart valve was formed from a PGA non-woven mesh solvent coated with P4HB. The P4HB coated scaffold was more stable in vitro than PGA alone, allowing the use of a pulsatile flow conditioning system and prolonged tissue maturation prior to implantation. After seeding with vascular cells and cell culture under dynamic flow conditions, a tissue engineered heart valve construct was formed that was suitable for implantation (see Fig. 6). After implantation in place of the native pulmonary valve, the tissue engineered heart valve functioned well, and echocardiography of the implanted valves demonstrated functioning mobile leaflets without any stenosis, thrombus, or aneurysm. Just 8 weeks after implantation into juvenile sheep it was reported that the scaffold composite had completely degraded, and by 20 weeks had been replaced with a new tissue engineered heart valve that closely resembled the native valve (see Fig. 7). Specifically,

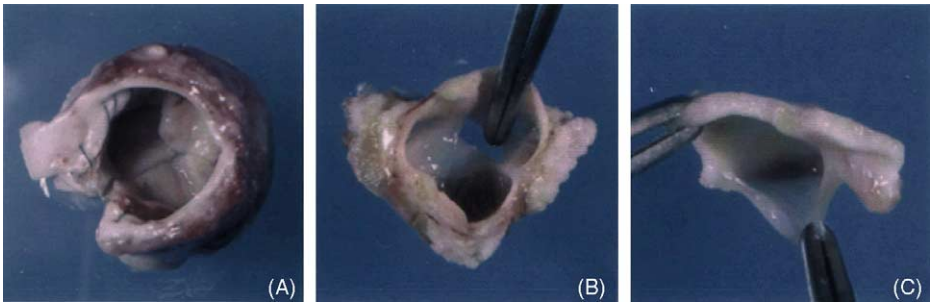

Fig. 7. Tissue engineered heart valve derived from P4HB/PGA composite explanted after: (A) 6 and (B) 20 weeks in vivo. (C) Note thin pliable leaflet at 20 weeks. Reproduced with permission from [13].

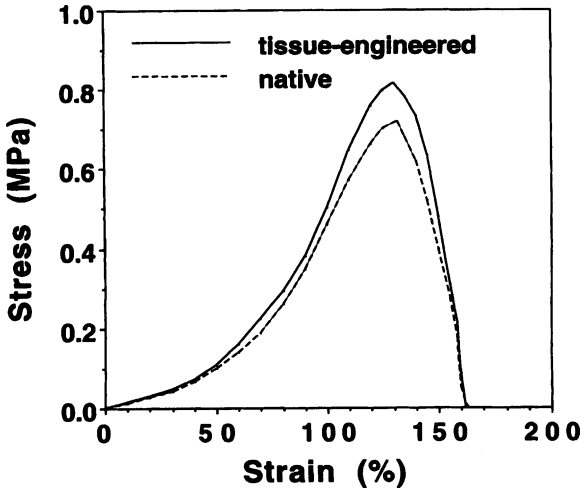

Fig. 8. Tensile mechanical properties of tissue engineered heart valve derived from P4HB/PGA composite explanted after 20 weeks in vivo and compared with native tissue. Reproduced with permission from [13].

(i) the tensile mechanical properties of the valve were almost indistinguishable from the native valve (see Fig. 8), (ii) biochemical analysis revealed a similar make up to the native counterpart, (iii) histological analysis of the leaflet structure (perhaps the most striking result) showed that the new structure was made up of three distinct organized layers, a fibrous layer of collagen, a loose layer rich in glycosaminoglycans (GAGs), and a layer of elastin that is characteristic of the native leaflet structure (see Fig. 9), and (iv) the size of the valve had increased from 19 mm at implant to 23 mm at 20 weeks as the lamb had grown. The latter is of course particularly exciting since it indicates that it should be possible to develop a valve for children that can grow, and not need replacing.

4.3. Vascular grafts

Vascular grafting is a common clinical procedure used to repair or replace compromised blood vessels, and it is estimated that over 500,000 of these procedures are performed in the US every year. Large diameter blood vessels are typically replaced with synthetic grafting materials, usually Dacron™ (polyethylene terephthalate) or expanded PTFE (ePTFE). However, these materials do not perform well when a small diameter graft is required as the grafts rapidly close (occlude). Instead, when surgeons perform procedures that require small diameter grafts, such as coronary bypass procedures, they typically harvest blood vessels (usually the saphenous vein or mammary artery) from the patient. Besides the obvious pain inflicted in these harvesting procedures, these autologous grafts can also be compromised or in short supply if the patient has had multiple procedures. (About 20% of bypass patients undergo subsequent surgeries.)

To overcome the current limitations in vascular grafting, efforts are underway to develop tissue engineered vascular grafts using a similar approach to that described above for the heart valve. Large diameter tubular conduits made of a PHO/PGA composite seeded with a mixed cell population of endothelial cells, smooth muscle cells, and fibroblasts (derived from carotid artery) have been investigated and used to replace 3–4 cm abdominal aortic segments in lambs [17]. Fairly recently a composite of P4HB and PGA, similar to that used in the heart valve studies, has been investigated as a potential vascular graft scaffold [18]. The composite was fashioned into tubular scaffolds with an internal diameter of 5 mm and a length of 4 cm, and seeded with ovine vascular myofibroblasts and endothelial cells. The seeded constructs were incubated in static culture for 4 days, and then subjected to pulsatile flow conditions with nutrient medium being directed immediately through the lumen (to simulate in vivo shear stress and radial distension of the vessel wall) for 4, 7, 14, 21, and 28 days before being subject to analysis. The latter revealed advanced tissue formation in an organized layered manner with smooth although not completely confluent surfaces and cells oriented in the direction of flow. It was speculated that premature exposure of the surfaces to high flow might have caused a partial detachment of endothelial cells. Nonetheless, cell mass and collagen content were both observed to increase up to 21 days. The grafts were found to develop burst strengths of over 300 mmHg by 28 days, and suture retention strengths appropriate for surgical implantation after 3 weeks.

4.4. Sutures and medical textile products

As mentioned earlier, P4HB can be elongated almost 10 times its original length. During this stretching process, the polymer chains become oriented, resulting in exceptionally strong fibers as shown in Table 3. These P4HB fibers are stronger than typical polypropylene sutures (410–460 MPa), and at least comparable in strength to commercial absorbable suture fibers like Maxon™ (540–610 MPa) and PDS II™ (450–560 MPa) sutures [20]. What may potentially set the P4HB suture fiber apart from current absorbable synthetic fibers is a lower Young's modulus equating with improved handling, and a different breaking strength retention profile upon implantation. The Young's modulus of oriented P4HB fiber (670 MPa), for example, is significantly lower than that of other monofilament sutures like Maxon™ (2930 MPa), PDSII™ (1380 MPa), and Biosyn™ (1000 MPa) [20].

Table 3
Mechanical properties of P4HB before and after orientation

Property	Compression molded	Oriented fiber[a]
Tensile strength (MPa)	50	545
Tensile modulus (MPa)	70	670
Elongation at break (%)	~1000	~60
Durometer hardness (Shore D)	52.8	NA

[a] Fiber diameter approximately 0.25 mm, representative of a 2/0 suture.

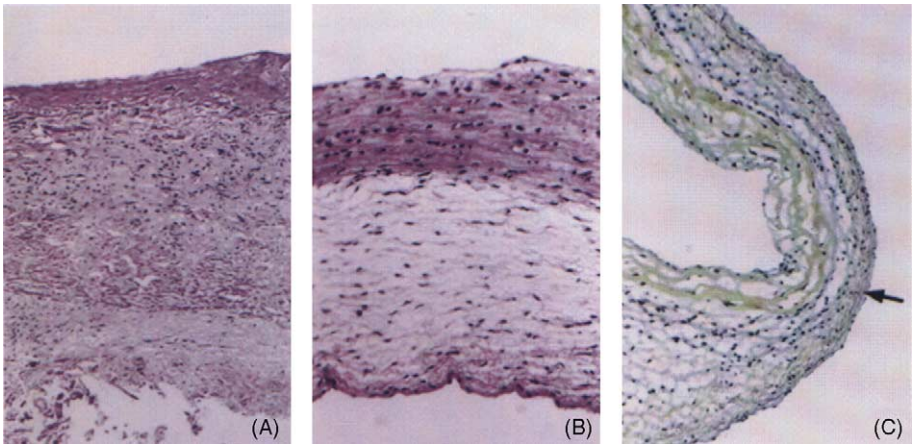

Fig. 9. Histology of tissue engineered heart valve leaflet derived from P4HB/PGA composite after explantation. (A) At 6 weeks, there is early organization of tissue predominantly in outer layer (top) (magnification 50×). (B) Cross-section of leaflet at 16 weeks shows layered cellular fibrous tissue, which is more dense near outflow surface (top) (magnification 100×). (C) Cross-section of leaflet at 20 weeks demonstrates collagen (yellow), GAGs (blue), and elastin (arrow, inflow surface; magnification 100×). Reproduced with permission from [13].

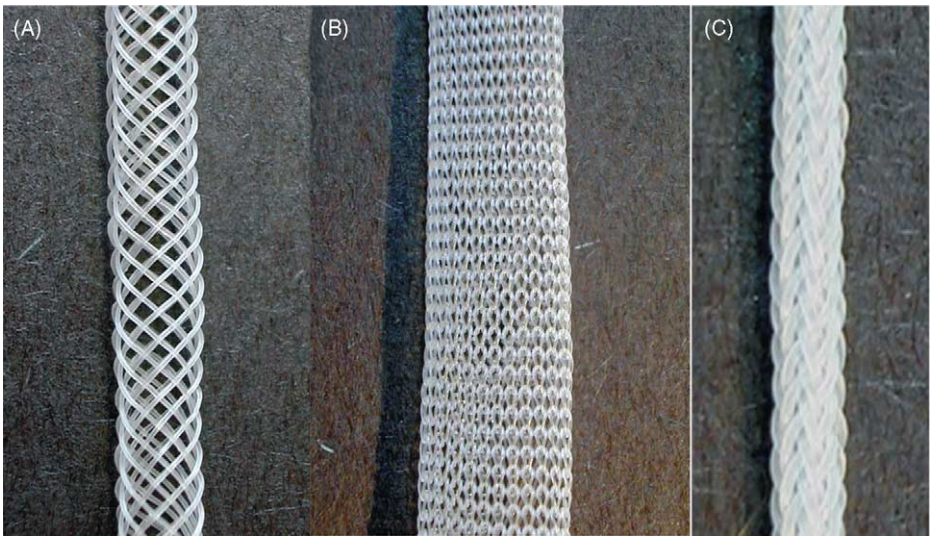

Fig. 10. P4HB textiles: (A) 16 filament braided tube; (B) circular knit tube; (C) 16 filament braid.

As well as potential use in suture applications, P4HB fibers and multifilament yarns with a range of properties can be produced to provide varied starting points for making medical textile based products such as grafts, patches, tissue engineering scaffolds, ligament, slings, surgical meshes, dura and pericardial substitutes. Several examples of textile products produced from P4HB fibers are shown in Fig. 10.

4.5. Bulking agents and soft tissue repair

Low molecular weight oligomers of P4HB have been prepared for potential use in soft tissue repair, augmentation, and bulking applications [21]. These oligomers were prepared in solution by hydrolysis of higher molecular weight P4HB, and along with P4HB microdispersions could potentially be administered by injection.

5. Conclusions

Early results indicate that P4HB is filling an unmet need as a new absorbable biomaterial offering a set of properties that are not currently available for medical product development (see Table 1). The biomaterial is far more flexible than existing options, and can elongate many times its original length setting it apart from available options, and opening up new possibilities for product development. Copolymers of 4HB with 3HB as shown in Table 2 will further extend the property range adding much needed absorbable elastomers.

Table 4
General properties of P4HB vs. PGA

Property	PGA	P4HB
Thermal properties	High melting temperature	Low melting temperature
Tensile strength	Very strong	Strong
Tensile modulus	Stiff	Flexible
Ability to elongate	Virtually none	High
Absorption rate	Very fast	Moderate
Loss of strength in vivo	Rapid	Gradual loss
Degradation products	Highly acidic	Less acidic
Inflammatory reaction	Can be severe for large implants	Well tolerated
Thermoplastic melt processing	Yes	Yes
Solvent processing	Virtually insoluble	Soluble in range of solvents
Resistance to moisture	Poor	Fairly good

Differences between P4HB and an existing offering, PGA, a biomaterial that is used extensively in tissue engineering, are summarized in Table 4 for comparison. Besides obvious differences in mechanical and thermal properties, these polymers degrade via different mechanisms that produce different outcomes. PGA degrades rapidly by a process that involves primarily diffusion of water into the polymer followed by bulk hydrolysis. In large PGA implants this can lead to the accumulation of highly acidic degradation products that can suddenly be released resulting in severe foreign body reactions [12]. It can also result in a dramatic loss of implant strength soon after implantation. In contrast, P4HB appears to be degraded in part by a surface erosion process in vivo that results in: (i) a gradual reduction of mechanical strength in vivo, and (ii) good biocompatibility due to a slow release of well tolerated less acidic degradation products. Moreover, P4HB, unlike PGA, is relatively stable to moisture even during processing, and has good shelf life. P4HB's greater stability to hydrolysis has also been put to good use in tissue engineering where it has been used in a bioreactor as a scaffold to support development of strong healthy tissues in vitro over prolonged periods, while PGA has failed under these same conditions due to rapid hydrolysis that results in disintegration of the scaffold.

Other PHA polymers, including PHO, P3HB, and its copolymers with other 3-hydroxyalkanoates, that further extend the range of properties available are also showing promise in medical applications development. For example, P3HB is currently being evaluated with some success for use in peripheral nerve repair [22], development of absorbable stents [23], and as patches for the repair of soft tissue defects [24]. These and others uses of PHAs in medical applications have been recently reviewed [25].

With a filing of a Device Master File for P4HB with the FDA, the first steps towards regulatory approval of medical products comprising P4HB have been completed. Efforts are now focusing on the development of the first medical products with this new absorbable material that take advantage of its unique properties.

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