(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 June 2008 (12.06.2008)

PCT

(10) International Publication Number
WO 2008/070428 A2

(51) International Patent Classification:
A61L 27/18 (2006.01) *A61L 31/06* (2006.01)
A61L 27/34 (2006.01) *A61L 31/10* (2006.01)

(21) International Application Number:
PCT/US2007/084991

(22) International Filing Date:
16 November 2007 (16.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/868,182 1 December 2006 (01.12.2006) US

(71) Applicant *(for all designated States except US)*: **TEPHA, INC.** [US/US]; 99 Hayden Avenue, Suite 360, Lexington, MA 02421 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RIZK, Said** [US/US]; 5 Castle Ridge Road, Salem, NH 03079 (US). **MARTIN, David, P.** [US/US]; 33 Hemlock Street, Arlington, MA 02474 (US). **HO, Kicherl** [KR/US]; 23 Champa Street, First Floor, Newton, MA 02464 (US). **WILLIAMS, Simon, F.** [GB/US]; 22 Cider Hill Lane, Sherborn, MA 01770 (US).

(74) Agents: **PABST, Patrea, L.** et al.; Pabst Patent Group Llp, 400 Colony Square, 1201 Peachtree Street, Suite 1200, Altanta, GA 30361 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/070428 A2

(54) **Title:** MEDICAL DEVICES CONTAINING ORIENTED FILMS OF POLY-4-HYDROXYBUTYRATE AND COPOLYMERS

(57) **Abstract:** Continuous processing methods for making absorbable polymeric films with one or more of the following properties: high toughness, low modulus, high tensile strength, and thickness less than 10 mm, more preferably less than 1 mm, and more preferably less than 100 μm, have been developed. In the preferred embodiment, the polymer is a polyhydroxyalkanoate, and in the most preferred embodiment, the polymer comprises 4-hydroxybutyrate. A particularly preferred embodiment is a film of poly-4-hydroxybutyrate or copolymer thereof, wherein the film has a tensile strength greater than 5.5 kgf/mm^2, tensile modulus less than 181 kgf/mm^2, and elongation at break from 10-500%, wherein the film is derived by a continuous process such as melt extrusion or solvent casting, followed by orientation to more than 25% of the film's original length in one or more directions. These can be used for a variety of purposes including fabrication of medical devices.

MEDICAL DEVICES CONTAINING ORIENTED FILMS OF POLY-4-HYDROXYBUTYRATE AND COPOLYMERS

Related Applications

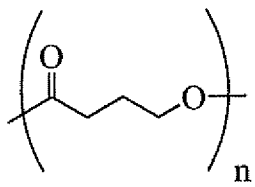
This application claims priority under 35 U.S.C. 119 to U.S.S.N. 60/868,182 filed December 1, 2006, *"Medical Devices Containing Oriented Films of Poly-4-Hydroxybutyrate and Copolymers"* by Said Rizk, David P. Martin, Kicherl Ho and Simon F. Williams.

Field of the Invention

The present invention generally relates to polymeric compositions that can be processed into films using continuous processes to produce products having substantially uniform physical properties, including physical and thermo-mechanical integrity. The compositions include polymers or copolymers comprising 4-hydroxybutyrate, and can be processed into films that are tough, have high strength and low modulus.

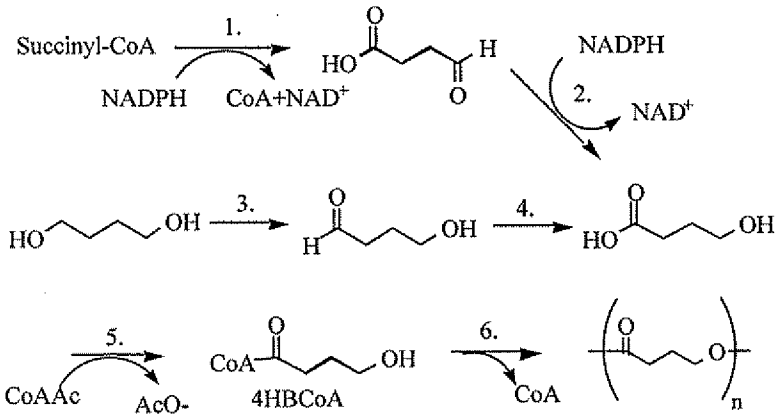
Background of the Invention

Poly-4-hydroxybutyrate (P4HB) and copolymers thereof can be produced using transgenic fermentation methods, see, for example, U.S. Patent No. 6,548,569 to Williams *et al.*, and are produced commercially, for example, by Tepha, Inc. (Cambridge, MA). Poly-4-hydroxybutyrate (P4HB, TephaFLEX® biomaterial) is a strong, pliable thermoplastic polyester that, despite its biosynthetic route, has a relatively simple structure



The polymer belongs to a larger class of materials called polyhydroxyalkanoates (PHAs) that are produced by numerous microorganisms (see, for example,: Steinbüchel A., et al. Diversity of Bacterial Polyhydroxyalkanoic Acids, *FEMS Microbial. Lett.* 128:219-228 (1995)). In nature these polyesters are produced as storage granules inside

cells, and serve to regulate energy metabolism. They are also of commercial interest because of their thermoplastic properties, and relative ease of production. Several biosynthetic routes are currently known to produce P4HB:



This schematic shows some of the known 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.

Chemical synthesis of P4HB has been attempted, but it has been impossible to produce the polymer with a sufficiently high molecular weight that is necessary for most applications (Hori, Y., et al., *Polymer* 36:4703-4705 (1995)).

U.S. Patent Nos 6,245,537, 6,623,748 and 7,244,442 describe methods of making PHAs with little to no endotoxin, which is suitable for medical applications. U.S. Patent Nos. 6,548,569, 6,838,493, 6,867,247, 7,268,205, and 7,179,883 describe use of PHAs to make medical devices. Copolymers of P4HB include 4-hydroxybutyrate copolymerized with 3-hydroxybutyrate or glycolic acid (U.S. patent application No. **20030211131** by Martin and Skraly, U.S. Patent No. 6,316,262 to Huisman *et al.*, and U.S. Patent No. 6,323,010 to Skraly *et al.*). Methods to control molecular weight of PHA polymers have been disclosed by U.S. Patent No. 5,811,272 to Snell *et al.*

PHAs with controlled degradation and degradation *in vivo* of less than one year are disclosed by U.S. Patent No. 6,548,569, 6,610,764, 6,828,357, 6,867,248, and 6,878,758 to Williams *et al.* and WO 99/32536 to Martin *et al.* Applications of P4HB have been reviewed in Williams, S.F., et al., *Polyesters, III*, 4:91-127 (2002), and by Martin, D. *et al.* Medical Applications of Poly-4-hydroxybutyrate: A Strong Flexible Absorbable Biomaterial, *Biochem. Eng. J.* 16:97-105 (2003). Medical devices and applications of P4HB have also been disclosed by WO 00/56376 to Williams *et al.*

Several patents including U.S. Patent Nos. 6,555,123, 6,585,994, and 7,025,980 describe the use of PHAs in tissue repair and engineering.

In the practice of surgery there currently exists a need for absorbable films with improved performance. These films can be used, for example, to reinforce tissue structures. They may also be used as anti-adhesion membranes, or as components of other devices. A number of other absorbable materials have been used to produce films for use in surgery. For example, films have been made from polylactic acid (PLA) or copolymers containing the different stereoisomers of lactic acid or glycolic acid. SurgiWrap™, for example, is a medical film implant made from a copolymer of L-lactide and D,L-lactide, 70:30. These materials do not, however, have ideal properties for many procedures and applications. Films made from PLA, like SurgiWrap™, have high modulus values, making them stiff, and preventing these films from contouring to bodily tissues when implanted. The high modulus values of PLA [see Gruber and O'Brien, 2002, in Biopolymers: Polyesters, III (Doi, Y. and Steinbüchel, A., Eds.) vol. 4, pp. 235-250. Weinheim: Wiley-VCH.] result in films of low toughness, and these properties, combined with other PLA properties, limit the ability of the polymer scientist to process PLA into thin films with good handling properties, for example, by solvent casting and melt extrusion.

U.S Patent No. 6,548,569 to Williams *et al.* discloses an unoriented film of poly-4-hydroxybutyrate produced by compression molding in a batch process, not a continuous process. The film had a tensile strength of 5.27

kgf/mm^2 (7,500 psi), tensile modulus of 6.6 kgf/mm^2 (9,400 psi), and elongation at break of 1,000%.

It is an object of the present invention to provide methods to produce films of absorbable polymers that have relatively low modulus values, and which are tough and have high strength.

It is a further object of the present invention to provide continuous processes to produce such films, such as melt processing and solvent casting, as compared to batch processes such as compression molding.

It is another object of the present invention to provide films which can be used in medical applications, for example, as implants such as devices for anti-adhesion barriers, tissue separation and temporary tissue support, coatings on medical devices, including stent coatings, as well as devices for tissue in-growth particularly where the film has been rendered porous.

It is therefore an object of the invention to provide continuous processes for polymer film production which yield materials with excellent physical and mechanical properties, and the resulting polymer films.

Summary of the Invention

Continuous processing methods for making absorbable polymeric films with one or more of the following properties: high toughness, low modulus, high tensile strength, and thickness less than 10 mm, more preferably less than 1 mm, and more preferably less than 100 μm, have been developed. In the preferred embodiment, the polymer is a polyhydroxyalkanoate, and in the most preferred embodiment, the polymer comprises 4-hydroxybutyrate. A particularly preferred embodiment is a film of poly-4-hydroxybutyrate or copolymer thereof, wherein the film has a tensile strength greater than 5.5 kgf/mm^2, tensile modulus less than 181 kgf/mm^2, and elongation at break from 10-500%, wherein the film is derived by a continuous process such as melt extrusion or solvent casting, followed by orientation to more than 25% of the film's original length in one or more directions.

These can be used for a variety of purposes including fabrication of medical devices.

Detailed Description of the Invention

Definitions

"Poly-4-hydroxybutyrate" as generally used herein means a homopolymer comprising 4-hydroxybutyrate units. It may be referred to herein as P4HB or TephaFLEX® biomaterial (manufactured by Tepha, Inc., Cambridge, MA).

"Copolymers of poly-4-hydroxybutyrate" as generally used herein means any polymer comprising 4-hydroxybutyrate with one or more different hydroxy acid units.

"Blend" as generally used herein means a physical combination of different polymers, as opposed to a copolymer comprised of two or more different monomers.

Orientation is the process by which the film is stretched beyond its yield point and plastically deformed, but does not break (i.e. it retains mechanical and physical integrity). The degree of orientation may be expressed as the percentage or ratio that the film is stretch when compared to the original film prior to orientation. Films are preferably oriented by stretching the film by at least 25% of the film's original length in one or more directions.

"Tensile modulus" is the ratio of stress to strain for a given material within its proportional limit. As used herein, low tensile modulus means a material having a tensile modulus less than 180 kgf/mm^2.

"Tensile strength" is the maximum or ultimate tensile load per unit area of original cross section area of the test specimen, within the gauge boundaries, sustained by the specimen during the test. As used herein, high tensile strength means a material test sample having a tensile strength of at least 5.3 kgf/mm^2.

"Toughness" means a property of a material by virtue of which it can absorb energy; the actual work per unit volume or unit mass of material that is required to rupture it. Toughness is usually proportional to the area under the load-elongation curve such as the tensile stress-strain curve. (Rosato's

Plastics Encyclopedia and Dictionary, Oxford Univ. Press, 1993.) As used herein, high toughness means a value greater than 10 kgf/mm^2.

"Elongation" or extensibility of a material means the amount of increase in length resulting from, as an example, the tension to break a specimen. It is expressed usually as a percentage of the original length. (Rosato's Plastics Encyclopedia and Dictionary, Oxford Univ. Press, 1993.)

"Molecular weight" as used herein, unless otherwise specified, refers to the weight average molecular weight (Mw), not number average molecular weight (Mn).

"Absorbable" as generally used herein means the material is broken down in the body and eventually eliminated from the body within five years.

"Biocompatible" as generally used herein means the biological response to the material or device being appropriate for the device's intended application *in vivo*. Any metabolites of these materials should also be biocompatible.

I. Composition

Methods have been developed to produce films of P4HB and copolymers with exceptional toughness. These methods may be used to prepare films that have substantially uniform physical properties and physical integrity. The methods may be run continuously, which is particularly advantageous in manufacturing. These films can be prepared by solution casting or by melt extrusion followed by orientation.

A. Polymers

The processes described herein can typically be used with any of the polyhydroxyalkanoate polymers, including blends and copolymers thereof.

In a preferred embodiment, the polymer is poly-4-hydroxybutyrate (P4HB) or a copolymer thereof. Copolymers include P4HB with 3-hydroxybutyrate, and P4HB with glycolic acid monomer. P4HB and copolymers thereof can be obtained from Tepha, Inc. of Cambridge, MA.

B. Films

In a preferred embodiment , films can be prepared with thickness of less than 10 mm, more preferably less than 1 mm, and even more preferably

less than 100 μm. It has been discovered that very thin films of P4HB polymer or copolymers thereof can be prepared with substantially uniform physical properties, and physical integrity, by solution casting. Using this method, films cast from solutions of the polymer or copolymers dissolved in organic solvents can have thicknesses that are less than 100 μm, and even less than 50 μm. For example, solution cast films of P4HB have been prepared with thicknesses of 20 to 50 μm. With appropriate choice of solvent, polymer and casting conditions, thinner films of P4HB can be produced, or the cast films can be stretched and oriented uniaxially or biaxially to yield thinner and stronger films than the unoriented cast films.

It has also been discovered that very thin films of P4HB and copolymer thereof can be prepared with exceptional toughness and strength. These cast films have a tensile strength of approximately 7.2 kgf/mm^2 and elongation to break of approximately 200%. In comparison, a commercially available implantable film of PLA (SurgiWrap™ Bioresorbable Film) has a tensile strength of approximately 5.9 kgf/mm^2 and an elongation to break of 95%.

Films of P4HB polymer or copolymers thereof, with exceptional toughness, can be prepared by melt processing followed by orientation (stretching). For example, a film of P4HB may be prepared by melt extrusion followed by stretching. Stretching substantially increases stress as measured in kgf/mm^2. For example, the stress in an unoriented P4HB film prepared by melt extrusion, thickness of 0.022 mm and width of 13 mm was measured on a MTS mechanical analyzer to be 4.98 kgf/mm^2. The stress in the same P4HB film after stretching the sample 3.6x the original length to a thickness of 0.010 mm and width of 8 mm was measured to be 14.13 kgf/mm^2 with an elongation to break of the oriented (or stretched) sample of approximately 25%.

Comparative ball burst testing can be done by ASTM D6797-02, [Standard Test Method for Bursting Strength of Fabrics Constant-Rate-of-Extension (CRE) Ball Burst Test (1 cm ball, 1.6 cm opening)]. This testing shows that P4HB films are stronger and tougher than SurgiWrap™ film,

another commercially available, absorbable film used as an implant material. Ball burst strength and elongation for a 40 μm P4HB film were 5.6 kgf and 39 mm (ball displacement at break), respectively, while for SurgiWrap they were 3.2 kgf and 3.4 mm (ball displacement at break), respectively, for a slightly thicker film (50 μm). The higher breaking force and longer extension to break for the P4HB film demonstrate its greater strength and toughness.

In a preferred embodiment, the films described herein have toughness greater than 10 kgf/mm^2, more preferably greater than 50 kgf/mm^2, and even more preferably greater than 100 kgf/mm^2.

In a preferred embodiment, the films described herein preferably have tensile strength greater than 5.5 kgf/mm^2, more preferably greater than 7.0 kgf/mm^2, and even more preferably greater than 10.0 kgf/mm^2.

In a preferred embodiment, the films described herein preferably have an elongation to break greater than 10%, more preferably greater than 15%, and even more preferably greater than 20%.

C. Other Components

The P4HB polymer and copolymer films may contain other materials, including plasticizers, nucleants, other polymers, additives, and compatibilizers. Examples of plasticizers are disclosed by U.S Patent No. 6,905,987 to Noda *et al.* Other components may be added to impart benefits such as, but not limited to, increased stability, including oxidative stability, brightness, color, flexibility, resiliency, workability, processibility (by addition of processing aids), viscosity modifiers, and odor control.

Active components, including therapeutic, diagnostic and/or prophylactic agents, such as drugs, or other substances may be incorporated. Such compositions may be used for controlled release of the drugs or other substances. These may be proteins, peptides, sugars, polysaccharides, glycoproteins, lipids, lipoproteins, nucleic acid molecules, or combinations thereof. Moreover, the films may comprise proteins, polysaccharides, peptides, as well as other substances including allograft and xenograft

materials. It may be advantageous to incorporate contrast agents, radiopaque markers, or radioactive substances.

For certain applications it may also be desirable to incorporate fillers, including materials such as titanium dioxide, calcium carbonate, hydroxyapatite, and tricalcium phosphate. Such fillers may include agents that can subsequently be leached or washed out of the film to render it porous.

D. Formation into Devices

Films made from P4HB polymers and copolymers thereof by solvent casting and melt extrusion are characterized by their thinness, which may be less than 100 μm, and even less than 50μm. These films are also characterized by high tensile strength and toughness and high ductility prior to orientation. These films have properties that are substantially improved for medical application relative to PLA-based films.

The films possess properties that are desirable in preparing medical products, particularly implantable medical devices. For example, the films may be used to make partially or fully absorbable biocompatible medical devices, or components thereof. Such devices include, but are not limited to: stent, stent graft, stent coating, drug delivery device, device for temporary wound or tissue support, repair patch, tissue engineering scaffold, retention membrane (for example, to retain bone graft), anti-adhesion membrane, tissue separation membrane, hernia repair device, device coating (including devices to improve fixation), cardiovascular patch, catheter balloon, vascular closure device, sling, biocompatible coating, rotator cuff repair device, meniscus repair device, adhesion barrier, guided tissue repair/regeneration device, articular cartilage repair device, nerve guide, tendon repair device, intracardiac septal defect repair device, including but not limited to atrial septal defect repair devices and PFO closure devices, left atrial appendage (LAA) closure device, pericardial patch, bulking and filling agent, vein valve, heart valve, bone marrow scaffold, meniscus regeneration device, ligament and tendon graft, ocular cell implant, spinal fusion device, imaging

device, skin substitute, dural substitute, bone graft substitute, wound dressing, and hemostat.

II. Methods of Manufacturing Films

A. Method of Making P4HB Polymer or Copolymer Films by Solvent Casting

In a preferred method, a film of P4HB polymer or copolymer thereof may be prepared by solution casting as follows. A homogeneous solution of P4HB in a suitable solvent such as 1,4-dioxane or tetrahydrofuran (THF) is prepared at approximately 10-15 wt/vol%. The solution should have a viscosity of approximately 400 to 7,400 cP. The polymer solution is pumped at approximately room temperature through a 150 mm slot die with a 400 μm die gap onto a moving web, for example, of aluminum foil. The web speed is approximately 0.5 m/min and traveled 5 m before being collected on a collection roller. The speed is adjusted to ensure evaporation of the solvent. One or more separate air drying zones set at 50-60°C were employed to remove solvent from the polymer film before collection on the final roll. A number of parameters can be varied to control the film thickness including, but not limited to, the pump speed, the die gap and width, the polymer concentration and the web speed.

B. Method of Making P4HB Polymer or Copolymer Films by Melt Processing through Melt Extrusion

Films can also be prepared by melt-extrusion methods. Preferred methods are a T-die extrusion method or an inflation method.

In the formation of the film by melt-extrusion, the barrel and T-die temperatures for preferably carrying out the formation are 80 to 250 °C, more preferably 100 to 210 °C. The melting of the P4HB is insufficient at temperature less than 100°C. When the temperature is higher than 250 °C, the P4HB markedly undergoes thermal decomposition. However, the site of the barrel directly below a hopper may have a temperature of less than 100 °C. The molten film exits the T-die and is cast over a chilled moving surface preferably, one or more rotating cylindrical cast rollers with surface temperature maintained at 5-100 °C, but more preferably at 10 °C. This step

is followed by a take-up step to wind up the extruded film. Film thickness can be varied by changing the gap of the T-die slit, polymer flow rate, and cast roll speed.

In the formation of film by the inflation method, an inflation molding circular die is used instead of a T-die to extrude cylindrical film of P4HB. The molten cylindrical film is cooled and solidified by blowing it up with cold air blown from the central portion of the circular die, and the cylindrical film which had been blown up is collected with a take-up machine. Film thickness can be varied by changing the gap of the inflation die slit, polymer flow rate, cooling air pressure and temperature and take-up speed.

C. Orientation of Films

The melt-extrusion films and solvent cast films show improved mechanical properties when stretched. The melt-extrusion film may be stretched by several methods such as a roll stretching and/or a stretching method using a tenter frame. The melt-extrusion film can be stretched at a temperature between room temperature and 150 °C at a stretch ratio of 0.25 to 15. To increase the processing rate, the stretching may be more preferably carried out at a temperature in the range of from 40 to 80 °C. The stretching may be monoaxial stretching for forming a monoaxially oriented film, consecutive biaxial stretching for forming a biaxially oriented film and simultaneous biaxial stretching for forming a plane-oriented film. When the melt-extrusion film is stretched, the tensile strength at break in the direction in which the film is stretched is increased.

The present invention will be further understood by referenced to the following non-limiting examples.

Example 1: Preparation of Solvent Cast P4HB Film by a Continuous Process

A homogeneous solution of P4HB in 1,4-dioxane (15% wt/vol) was prepared by dissolving 91 g of P4HB in 610 ml of 1,4-dioxane. This solution had a viscosity of approximately 7,400 cP. The polymer solution was pumped at approximately 36 ml/min at room temperature through a 150 mm slot die with a 400 μm die gap onto a moving web of aluminum foil.

The web speed was approximately 0.5 m/min and traveled 5 m before being collected on a collection roller. Three separate air drying zones set at 50-60°C were employed to desolventize the polymer film before collection on the final roll. Using these conditions, a 43 μm thick film was obtained. A thinner film (24 μm thick) was obtained by increasing the web speed to 0.75 m/min and reducing the polymer concentration to 10%. Thinner films may also be obtained by reducing the die gap or pump speed. Mechanical properties of the solvent cast films compared to commercially available SurgiWrap™ 70:30 Poly (L-lactide-co-D,L-lactide) are shown in Tables 1 and 2.

Table 1. Tensile mechanical properties of solvent cast P4HB films versus SurgiWrap™ Bioresorbable Film.

Description	Thickness (mm)	Tensile Strength (kgf/mm^2)	Elongation at break (%)	Tensile Modulus (kgf/mm^2)
P4HB Solvent Cast Film	0.043	7.2	238	93
P4HB Solvent Cast Film	0.024	5.6	186	102
SurgiWrap™ 70:30 Poly (L-lactide-co-D,L-lactide)	0.050	5.0	95	181

Table 2. Ball burst properties of solvent cast P4HB film and SurgiWrap™ Bioresorbable Film. (1.0 cm ball, 1.6 cm opening, 300 mm/min ball speed per ASTM D6797-2)

Description	Thickness (mm)	Peak Load (kg)	Ball displacement at break (mm)
P4HB Solvent Cast Film	0.040	5.6	39
P4HB Solvent Cast Film	0.024	4.3	43
SurgiWrap™	0.050	3.2	3.4

Example 2: Preparation of a P4HB Film by Extrusion Casting and Stretching

P4HB (Tepha, Inc., Cambridge, MA) (Mw 506,000) was ground into small pieces using a Fritsch cutting mill (Pulversette 15, 10 mm bottom sieve) and dried under vacuum overnight to less than 0.01% (w/w) water. Dried pellets of the polymer were fed into an extruder barrel of a Leistritz 27 mm, 40:1 L/D co-rotating twin screw extruder fitted with 10 inch wide coat-hanger die with adjustable die lips initially set at 0.015 inch gap. Eleven heating zones of the extruder were set at 75, 90, 110, 110, 130, 130, 130, 150, 150, 200 and 200 °C and the die temperature was set at 200 °C. Polymer feed rate was set at 1 lb/hr and the extruder speed was set at 100 rpm. Melt pressure measured 247 psi and melt temperature measured 208 °C. A 7-inch diameter roll was used for casting. Roll surface temperature was kept at 12 °C and film line speed was maintained at 3 feet per minute. The properties of a film derived by this process before and after biaxial orientation is shown in Table 3.

Table 3 Tensile mechanical properties of P4HB film produced by a melt extrusion process before and after orientation

Specimen	Thickness (mm)	Width (mm)	Load (kgf)	Tensile Stress (kgf/mm^2)	Elongation at Break (%)	Tensile Modulus (kgf/mm^2)	Toughness (kgf/mm^2)
Unoriented	0.035	8	1.00	5.72	515	27.8	1511
Unoriented	0.061	8	1.56	5.10	561	31.8	1488
Unoriented	0.230	8	6.35	5.63	1191	23.4	3747
Biaxially Oriented	0.010	8	1.13	14.13	25.0	22.5	184

Example 3: Comparative Data for Commercial Films

Tables 4 and Table 5 below illustrate the advantageous mechanical properties of P4HB films prepared by the methods described herein. Their tensile properties are compared with films made from an absorbable polymer, L-PLA (L-polylactic acid), unoriented P4HB films produced in this work and with unoriented P4HB films produced in a batch process.

Table 4 Tensile Property Comparison

Samples	Tensile Strength	Elongation at Break	Tensile Modulus	Toughness
	kgf/mm^2	%	kgf/mm^2	kgf/mm^2
P4HB Unoriented Film, Batch Process See US Patent 6,548,569	5.27	1,000	66.0	N/A
P4HB Melt Extruded Unoriented (Average values from Table 3)	5.48	500-1200	27.7	2249
P4HB Biaxially oriented	14.13	25.0	22.5	184.0
PLLA Film	6.32	1.50	745.6	3.875

Table 5 Ball Burst Strength Comparison (1.0 inch ball, 1.75 inch opening, 300 mm/min ball speed per ASTM D6797-2)

Samples	Thickness	Burst Load	Burst Stress	Ball displacement at break
	mm	kgf	kgf/mm^2	mm
P4HB Melt Extruded Unoriented	0.036	16.14	14.28	95.3
P4HB Melt Extruded Unoriented	0.059	19.13	11.71	87.6
P4HB Melt Extruded Unoriented	0.226	70.42	9.92	83.0
P4HB Biaxially Oriented	0.01	3.6	7.22	22.7
PLLA film	0.100	4.5	1.88	3.3
SurgiWrap	0.046	5.38	3.72	5.7

5

We claim:

1. A film of poly-4-hydroxybutyrate or copolymer thereof, wherein the film has a tensile strength greater than 5.5 kgf/mm^{2}and wherein the film is derived by a continuous process, followed by orientation such that the film is stretched by more than 25% of the film's original length in one or more directions.

2. The film of claim 1 formed by melt extrusion or solvent casting.

3. The film of claim 1, wherein the film has a tensile strength greater than 5.5 kgf/mm^2, and elongation at break from 10-500%, wherein the film is derived by melt extrusion or solvent casting, followed by orientation such that the film is stretched by more than 25% of the film's original length in one or more directions.

4. The film of claim 1 formed into a device.

5. The film of claim 4 in the form of a device selected from the group consisting of a stent, stent graft, stent coating, drug delivery device, device for temporary wound or tissue support, repair patch, tissue engineering scaffold, retention membrane, anti-adhesion membrane, tissue separation membrane, hernia repair device, device coating, cardiovascular patch, catheter balloon, vascular closure device, sling, biocompatible coating, rotator cuff repair device, meniscus repair device, adhesion barrier, guided tissue repair/regeneration device, articular cartilage repair device, nerve guide, tendon repair device, intracardiac septal defect repair device, including but not limited to atrial septal defect repair devices and PFO closure devices, left atrial appendage (LAA) closure device, pericardial patch, bulking and filling agent, vein valve, heart valve, bone marrow scaffold, meniscus regeneration device, ligament and tendon graft, ocular cell implant, spinal fusion device, imaging device, skin substitute, dural substitute, bone graft substitute, wound dressing, and hemostat.

6. The film of claim 1, wherein the thickness of the film is less than 10.0 mm, more preferably less than 1.0 mm, and even more preferably less than 100 μm.

7. The film of claim 1 further comprising a prophylactic, diagnostic, or therapeutic agents.

8. The film of claim 1 further comprising additives selected from the group consisting of other polymers, plasticizers, nucleants, compatibilizers, porogens, radiolabelled substances, imaging agents, radiopaque markers, contrast agents, anti-oxidants, dyes, viscosity modifiers, and/or odor control agents.

9. A method of producing a film of poly-4-hydroxybutyrate or copolymer thereof, wherein the film has a tensile strength greater than 5.5 kgf/mm^{2}and wherein the film is derived by a continuous process of solvent casting or melt extrusion of the polymer to form a film, followed by orientation of the film such that the film is stretched by more than 25% of the film's original length in one or more directions.

10. The method of claim 9 further comprising forming the film into a device selected from the group consisting of a stent, stent graft, stent coating, drug delivery device, device for temporary wound or tissue support, repair patch, tissue engineering scaffold, retention membrane, anti-adhesion membrane, tissue separation membrane, hernia repair device, device coating, cardiovascular patch, catheter balloon, vascular closure device, sling, biocompatible coating, rotator cuff repair device, meniscus repair device, adhesion barrier, guided tissue repair/regeneration device, articular cartilage repair device, nerve guide, tendon repair device, intracardiac septal defect repair device, including but not limited to atrial septal defect repair devices and PFO closure devices, left atrial appendage (LAA) closure device, pericardial patch, bulking and filling agent, vein valve, heart valve, bone marrow scaffold, meniscus regeneration device, ligament and tendon graft, ocular cell implant, spinal fusion device, imaging device, skin substitute, dural substitute, bone graft substitute, wound dressing, and hemostat.

11. A method of using a device formed of a film of poly-4-hydroxybutyrate or copolymer thereof, wherein the film has a tensile strength greater than 5.5 kgf/mm^{2}and wherein the film is derived by a continuous process of solvent casting or melt extrusion of the polymer to form a film, followed by orientation of the film such that the film is stretched by more than 25% of the film's original length in one or more directions comprising inserting or implanting the device into an individual in need thereof.

12. The method of claim 11 wherein the device is selected from the group consisting of a stent, stent graft, stent coating, drug delivery device, device for temporary wound or tissue support, repair patch, tissue engineering scaffold, retention membrane, anti-adhesion membrane, tissue separation membrane, hernia repair device, device coating, cardiovascular patch, catheter balloon, vascular closure device, sling, biocompatible coating, rotator cuff repair device, meniscus repair device, adhesion barrier, guided tissue repair/regeneration device, articular cartilage repair device, nerve guide, tendon repair device, intracardiac septal defect repair device, including but not limited to atrial septal defect repair devices and PFO closure devices, left atrial appendage (LAA) closure device, pericardial patch, bulking and filling agent, vein valve, heart valve, bone marrow scaffold, meniscus regeneration device, ligament and tendon graft, ocular cell implant, spinal fusion device, imaging device, skin substitute, dural substitute, bone graft substitute, wound dressing, and hemostat.