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# DESCRIPTION

## BACKGROUND OF THE INVENTION

### Field of the Invention

[0001] This invention relates to methods of treatment of blood vessels with bioabsorbable polymeric medical devices, in particular, stents.

### Description of the State of the Art

[0002] This invention relates to radially expandable endoprostheses, that are adapted to be implanted in a bodily lumen. An "endoprosthesis" corresponds to an artificial device that is placed inside the body. A "lumen" refers to a cavity of a tubular organ such as a blood vessel. A stent is an example of such an endoprosthesis. Stents are generally cylindrically shaped devices that function to hold open and sometimes expand a segment of a blood vessel or other anatomical lumen such as urinary tracts and bile ducts. Stents are often used in the treatment of atherosclerotic stenosis in blood vessels. "Stenosis" refers to a narrowing or constriction of a bodily passage or orifice. In such treatments, stents reinforce body vessels and prevent restenosis following angioplasty in the vascular system. "Restenosis" refers to the reoccurrence of stenosis in a blood vessel or heart valve after it has been treated (as by balloon angioplasty, stenting, or valvuloplasty) with apparent success.

[0003] Stents are typically composed of scaffolding that includes a pattern or network of interconnecting structural elements or struts, formed from wires, tubes, or sheets of material rolled into a cylindrical shape. This scaffolding gets its name because it physically holds open and, if desired, expands the wall of the passageway. Typically, stents are capable of being compressed or crimped onto a catheter so that they can be delivered to and deployed at a treatment site.

[0004] Delivery includes inserting the stent through small lumens using a catheter and transporting it to the treatment site. Deployment includes expanding the stent to a larger diameter once it is at the desired location. Mechanical intervention with stents has reduced the rate of restenosis as compared to balloon angioplasty. Yet, restenosis remains a significant problem. When restenosis does occur in the stented segment, its treatment can be challenging, as clinical options are more limited than for those lesions that were treated solely with a balloon.

[0005] Stents are used not only for mechanical intervention but also as vehicles for providing biological therapy. Biological therapy uses medicated stents to locally administer a therapeutic substance. The therapeutic substance can also mitigate an adverse biological response to the presence of the stent. Effective concentrations at the treated site require systemic drug administration which often produces adverse or even toxic side effects. Local delivery is a preferred treatment method because it administers smaller total medication levels than systemic methods, but concentrates the drug at a specific site. Local delivery thus produces fewer side effects and achieves better results.

[0006] A medicated stent may be fabricated by coating the surface of either a metallic or polymeric scaffolding with a polymeric carrier that includes an active or bioactive agent or drug. Polymeric scaffolding may also serve as a carrier of an active agent or drug.

[0007] The stent must be able to satisfy a number of mechanical requirements. The stent must have sufficient radial strength so that it is capable of withstanding the structural loads, namely radial compressive forces, imposed on the stent as it supports the walls of a vessel. Once expanded, the stent must adequately provide lumen support during a time required for treatment in spite of the various forces that may come to bear on it, including the cyclic loading induced by the beating heart. In addition, the stent must possess sufficient flexibility with a certain resistance to fracture.

[0008] Stents made from biostable or non-erodible materials, such as metals, have become the standard of care for percutaneous coronary intervention (PCI) as well as in peripheral applications, such as the superficial femoral artery (SFA), since such stents have been shown to be capable of preventing early and later recoil and restenosis.

[0009] In order to effect healing of a diseased blood vessel, the presence of the stent is necessary only for a limited period of

time. There are certain disadvantages to the presence of a permanent implant in a vessel such as compliance mismatch between the stent and vessel and risk of embolic events. To alleviate such disadvantages, stent can be made from materials that erode or disintegrate through exposure to conditions within the body. Thus, erodible portions of the stent can disappear from the implant region after the treatment is completed, leaving a healed vessel. Stents fabricated from biodegradable, bioabsorbable, and/or bioerodable materials such as bioabsorbable polymers can be designed to completely erode only after the clinical need for them has ended.

**[0010]** Like a durable stent, a biodegradable stent must meet time dependent mechanical requirements. For example, it must provide patency for a minimum time period. However, it is also important for a biodegradable stent to completely degrade from the implant site within a certain period of time. A biodegradable material that can provide the mechanical requirements may not possess the requisite or desired degradation time. In addition, the requisite or desired degradation time varies between types of applications, i.e. coronary or peripheral.

**[0011]** EP 1 184 008 A1 discloses: stent for treating a diseased section of a blood vessel, comprising: a polymeric scaffolding consisting of poly(L-lactide), wherein the crystallinity of the poly(L-lactide) is between 15-60%, and wherein the weight average molecular weight of the poly(L-lactide) is between 60,000 and 300,000, relative to polystyrene standards. US 2007/253999 and WO 2007/146354 A2 disclose biodegradable poly (L-lactide) stents.

**[0012]** BENDIX D: "Chemical synthesis of polylactide and its copolymers for medical applications", POLYMER DEGRADATION AND STABILITY, BARKING, GB, discloses that monomers of L-lactide in PLLA are considered impurities that lead to severe (rapid) degradation during thermal processing.

### **SUMMARY OF THE INVENTION**

**[0013]** Various embodiments of the present invention include a stent for treating a diseased section of a blood vessel, comprising: a polymeric scaffolding comprising poly(L-lactide) and between 0.05 wt% and 0.5 wt% L-lactide monomer mixed, dispersed, or dissolved within the poly(L-lactide), wherein the crystallinity of the poly(L-lactide) is between 20-50%, and wherein the number average molecular weight of the poly(L-lactide) is between 60,000 and 300,000, relative to polystyrene standards.

**[0014]** Further embodiments of the present invention includes a method of treating a diseased section of a blood vessel, comprising: deploying a bioabsorbable polymeric stent at a diseased section of a blood vessel the stent comprising a body including a scaffolding composed of a pattern of struts, wherein the body is composed of poly(L-lactide) and between 0.05 and 0.5% L-lactide monomer, wherein the stent supports the vessel wall at or near a deployment diameter for a period of support which is followed by a decline in radial strength of the stent such that the stent is unable to support the vessel wall, wherein the scaffolding breaks apart and is completely absorbed away into the human body.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

**[0015]**

FIG. 1 depicts an exemplary stent.

FIG. 2 depicts a plot of the *in vitro* degradation behavior for a PLLA stent with different concentrations of L-lactide monomer.

FIG. 3 depicts a plot of a degradation rate constants versus L-lactide monomer concentration based on the data of FIG. 2.

### **DETAILED DESCRIPTION OF THE INVENTION**

**[0016]** Coronary arteries refer generally to arteries that branch off the aorta to supply the heart muscle with oxygenated blood. Peripheral arteries refer generally to blood vessels outside the heart and brain.

**[0017]** In both coronary artery disease and peripheral artery disease, the arteries become hardened and narrowed or stenotic and restrict blood flow. In the case of the coronary arteries, blood flow is restricted to the heart, while in the peripheral arteries

blood flow is restricted leading to the kidneys, stomach, arms, legs, and feet. The narrowing is caused by a the buildup of cholesterol and other material, called plaque, on the inner walls of the vessel. Such narrowed or stenotic portions are often referred to as lesions. Artery disease also includes the reoccurrence of stenosis or restenosis that occurs after an angioplasty treatment. Although there are probably several mechanisms that lead to restenosis of arteries, an important one is the inflammatory response, which induces tissue proliferation around an angioplasty site. The inflammatory response can be caused by the balloon expansion used to open the vessel, or if a stent is placed, by the foreign material of the stent itself.

**[0018]** Embodiments of the present invention are applicable to treatment of coronary and peripheral disease in coronary arteries and various peripheral vessels including the superficial femoral artery, the iliac artery, and carotid artery. The embodiments are further applicable to various stent types, such as self-expandable and balloon expandable stents. The embodiments are further applicable to various stent designs including scaffolding structures formed from tubes, wire structures, and woven mesh structures.

**[0019]** In embodiments of the present invention, a stent includes a plurality of cylindrical rings connected or coupled with linking elements. When deployed in a section of a vessel, the cylindrical rings are load bearing and support the vessel wall at an expanded diameter or a diameter range due to cyclical forces in the vessel. Load bearing refers to the supporting of the load imposed by radial inwardly directed forces. Structural elements, such as the linking elements or struts, are non-load bearing, serving to maintain connectivity between the rings. For example, a stent may include a scaffolding composed of a pattern or network of interconnecting structural elements or struts.

**[0020]** FIG. 1 depicts a view of an exemplary stent 100. In some embodiments, a stent may include a body, backbone, or scaffolding having a pattern or network of interconnecting structural elements 105. Stent 100 maybe formed from a tube (not shown). FIG. 1 illustrates features that are typical to many stent patterns including cylindrical rings 107 connected by linking elements 110. As mentioned above, the cylindrical rings are load bearing in that they provide radially directed force to support the walls of a vessel. The linking elements generally function to hold the cylindrical rings together.

**[0021]** The structural pattern in FIG. 1 is merely exemplary and serves to illustrate the basic structure and features of a stent pattern. A stent such as stent 100 may be fabricated from a polymeric tube or a sheet by rolling and bonding the sheet to form the tube. A tube or sheet can be formed by extrusion or injection molding. A stent pattern, such as the one pictured in FIG. 1, can be formed on a tube or sheet with a technique such as laser cutting or chemical etching. The stent can then be crimped on to a balloon or catheter for delivery into a bodily lumen.

**[0022]** The prevailing mechanism of degradation of biodegradable polymer is chemical hydrolysis of the hydrolytically unstable backbone. In a bulk eroding polymer, polymer is chemically degraded and material is lost from the entire polymer volume. As the polymer degrades, the molecular weight decreases. The reduction in molecular weight is followed by a reduction in mechanical properties, and then erosion or mass loss. The decrease in mechanical properties eventually results in loss of mechanical integrity demonstrated by fragmentation of the device. Enzymatic attack and metabolization of the fragments occurs, resulting in a rapid loss of polymer mass.

**[0023]** The treatment of artery disease with a stent of the present invention has time dependent properties once it is implanted which enable the treatment and healing of a diseased section of the vessel. In particular, the molecular weight, the mechanical properties, the mechanical integrity, and mass change with time. After deployment at a diseased section artery, the stent supports the section at an increased diameter for a period of time. Due a decrease in molecular weight, the radial strength degrades to the point that the stent can no longer support the walls of the section of the vessel. "Radial strength" of a stent is defined as the pressure at which a stent experiences irrecoverable deformation. The loss of radial strength is followed by a gradual decline of mechanical integrity.

**[0024]** Mechanical integrity refers to the size, shape, and connectivity of the structural elements of the stent. For example, the shape refers to the generally tubular shape of the stent formed by the cylindrically-shape rings connected by the linking elements of the pattern. Mechanical integrity starts to be lost when fractures appear or propagate in structural elements of the stent due to chemical degradation (molecular weight decline). Further loss of mechanical integrity occurs when there is breaking or loss of connectivity in structural elements.

**[0025]** The initial clinical need for any stent is to provide mechanical support to maintain patency or keep a vessel open at or near the deployment diameter. The patency provided by the stent allows the stented segment of the vessel to undergo positive remodeling at the increased deployed diameter. By maintaining the patency of the stented segment at this stage, the stent prevents negative remodeling. Remodeling refers generally to structural changes in the vessel wall that enhance its load-bearing ability so that the vessel wall in the stented section can maintain an increased diameter in the absence of the stent support. A

period of patency is required in order to obtain permanent positive remodeling.

**[0026]** During this time period, the stent inhibits or prevents the natural pulsatile function of the vessel. The stent structure prevents recoil and maintains a circular lumen while the vessel remodels and molds itself to the stented diameter, which corresponds to positive remodeling. Early recoil before sufficient modeling takes place can result in negative remodeling, referring to molding of the stent to a diameter significantly less than the original stented diameter, for example, 50% or less than the original deployment diameter.

**[0027]** As the polymer of the stent degrades, the radial strength of the stent decreases and the load of the vessel is gradually transferred from the stent to the remodeled vessel wall. Remodeling of the vessel wall continues after loss of radial strength of the stent. Before the stent loses mechanical integrity, it is desirable for the stent structural elements to become incorporated in the vessel wall by an endothelial layer. The stent then breaks apart which allows vasomotion. The vessel wall continues to remodel as the vessel moves due to vasomotion. The stent eventually erodes away completely leaving a healed vessel with an increased diameter and which can exhibiting vasomotion the same or similar to a healthy vessel section.

**[0028]** Poly(L-lactide) (PLLA) is attractive as a stent material due to its relatively high strength and a rigidity at human body temperature, about 37 °C. Since it has glass transition temperature between about 60 and 65 °C (Medical Plastics and Biomaterials Magazine, March 1998), it remains stiff and rigid at human body temperature. This property facilitates the ability of a stent to maintain a lumen at or near a deployed diameter without significant recoil.

**[0029]** PLLA has an *in vitro* degradation time of up to 3 years (Medical Plastics and Biomaterials Magazine, March 1998; Medical Device Manufacturing & Technology 2005). The degradation time is the time required for complete loss of mass of a polymer construct, such as a stent. The degradation time *in vivo* is shorter and depends on the animal model. In addition to an erosion profile, a PLLA stent has associated molecular weight and mechanical property (e.g., strength) profiles. As demonstrated above, the time dependence of the mechanical properties and mechanical integrity are important in the treatment of a diseased vessel. The degradation properties of PLLA do not generally coincide with what is required or desired for a particular treatment application. For example, it is desirable for a PLLA stent to have a degradation time of about two years (e.g., 22 to 26 months) for coronary vascular application, of about eighteen months (e.g., 16-20 months) for a peripheral application (e.g., superficial femoral artery (SFA)), and less than a year for nasal applications. For coronary and peripheral applications, the radial strength should be maintained for between one to six months, wherein maintaining radial strength refers to the ability of the stent to maintain the stented section at a diameter at least 50% of the original deployed diameter. For coronary and peripheral applications, the start of the loss of mechanical integrity should not occur until at least between 2 and 4 months, where the start of the loss of mechanical integrity corresponds to breaking apart of structural elements.

**[0030]** It is desirable to adapt a PLLA stent to various applications, so that it has the degradation behavior appropriate to each application, without significantly changing the composition of the stent. The embodiments of the present invention relate to adjusting the time-dependent degradation behavior of a PLLA stent through inclusion L-lactide (LLA) monomer in a stent body composed of PLLA.

**[0031]** The embodiments of the stent can include a body or scaffolding that is composed of PLLA with a targeted small amount of LLA monomer. The body can be composed of targeted amount of LLA and the rest of the body can be 100% PLLA. Additionally, the body can be made of the targeted amount of LLA, additional components, and the rest of the body 100% PLLA. The body can be 95 wt% or greater and the rest of the body the targeted amount of LLA and optionally the additional components. The additional components can be drugs, polymers, or filler materials such as bioceramic particles. The present invention includes embodiments that exclude additional components or exclude one or more of the additional components mentioned above.

**[0032]** In additional embodiments, the PLLA stent body can include additionally or alternatively, d-lactide, meso-lactide, glycolide, lactic acid, or their oligomers with an Mn less than 1,000 g/mol. The concentration of these additional monomers can be the same as those disclosed for L-lactide.

**[0033]** The stent can further include a coating over the body or scaffolding. In one embodiment, the coating can be a polymer and drug mixture. For example, the coating can be poly(DL-lactide) and the drug could be an antiproliferative such as everolimus. The coating can be free of the LLA monomer other than incidental migration or diffusion of LLA into the coating.

**[0034]** Low molecular weight PLLA oligomers can also increase the degradation rate, and thus adjust degradation behavior. However, the increase is primarily due to acidic end groups that act as catalysts to increase degradation rate of the PLLA. Thus, the larger the oligomer, a higher the weight fraction of oligomer in the PLLA that is required. Therefore, a much lower weight

fraction of LLA monomer than given oligomer is required for a similar effect as the oligomer. The high weight fraction of oligomer can negatively impact the mechanical properties of the stent.

**[0035]** The qualitative and precise effect of LLA monomers on PLLA on degradation behavior is not known. For example, the amount required monomer required to obtain desired degradation behavior is not. This can be at least partially attributed to the fact that the degradation behavior of a stent made from a semicrystalline degradable polyester, such as PLLA, is a complex function of several properties of the material and stent body. These properties include the intrinsic hydrolysis rate of the polymer (i.e., the chain scission reactions of the polymer backbone), the degree of crystallinity, the morphology (size and distribution of crystallite domains in the amorphous matrix), molecular weight (as measured by the inherent viscosity, number or weight average molecular weight), and stent body parameters (pattern, strut dimensions).

**[0036]** A semicrystalline polymer generally may have insufficient strength and fracture toughness to provide adequate and safe treatment of a blood vessel. The fabrication of the stent of present invention includes processing which increases the strength and fracture toughness of the final stent product. This processing provides certain characteristics that effect the degradation behavior, e.g., crystallinity, morphology. The strength and fracture toughness are increased by induced biaxial orientation of polymers in the hoop or circumferential and axial direction, a particular range of the degree of crystallinity, and small dispersed crystallites.

**[0037]** The stent is made from an extruded PLLA polymer tube that has been radially expanded and axially stretched to provide the induced orientation. The polymer tube is expanded by blow molding with a percent radial expansion between 200% and 500%, and a percent axial stretch from 20% to 200%. The extruded PLLA tubing has a percent of axial stretch from 100% to 400%. The stent is formed from the expanded tube by laser cutting the tubing in its expanded state.

**[0038]** Additionally, the blow molding process is performed in a manner that result in small crystallites dispersed through an amorphous matrix. Prior to expansion, the tube is heated to a temperature between 65 °C and 75 °C to induce formation of smaller crystallites that enhance fracture toughness. The tube is quenched below the glass transition temperature ( $T_g$ ) after expansion to prevent further crystal growth. The degree of crystallinity is 20-50%. Below 20% crystallinity the stent body may not be have sufficient strength, while above 50% crystallinity the stent body may be too brittle. The number average molecular weight ( $M_n$ ) of scaffolding material in the final product (in g/mol) is between 60,000 and 300,000, or more narrowly between 80,000 and 200,000.

**[0039]** An exemplary strut cross-section can be rectangular, for example, 140 x 140  $\mu\text{m}$  to 160 x 160  $\mu\text{m}$  or having a cross-sectional area between 20,000 and 25,000  $\mu\text{m}^2$ . As shown below, it is expected that an LLA content of greater than 1 wt% or greater than 2 wt% will result in a stent that does not maintain radial strength and mechanical strength long enough for effective treatment of a diseased section of a vessel.

**[0040]** The LLA monomer can be dispersed in the form of a powder or particular particles through all or a portion of a stent body. The size of such particles can be less than 100 nm, between 100 nm and 1000 nm, or greater than 1000 nm, where size can refer to diameter or some other characteristic length. Alternatively, the LLA monomer can be mixed or dissolved on a molecular level with the PLLA.

**[0041]** It has been observed from *in vitro* and *in vivo* degradation studies of PLLA stents with L-lactide monomer, discussed below, that LLA provides a dramatic and unexpected increase in the degradation rate of the stent, particularly above about 1 wt%. Stents having monomer compositions above about 1 wt% LLA lose mechanical strength, lose mechanical integrity, and erode away too fast for effective treatment in coronary and peripheral applications. Additionally, the low concentration of LLA are advantageous since the effect of the dispersed monomer in the polymer has no or a minimal effect on the mechanical properties of the polymer.

**[0042]** Additionally, it is important that the LLA monomer be uniformly or substantially uniformly dispersed through the PLLA of the stent to provide uniform degradation behavior through the body of the stent. It has been observed that for such low concentrations of LLA monomer, the uniformity of distribution is highly dependent on the manner of mixing or dispersing of the LLA. Thus, additional embodiments include a method of mixing the LLA in the PLLA stent material.

**[0043]** *In vitro* and *in vivo* studies of degradation behavior can be used to assess the influence of LLA monomer concentration on the degradation behavior of a PLLA stent. In addition, the influence can be assessed using theoretical models.

**[0044]** A hydrolytic degradation model for aliphatic polyesters having the form  $M_n(t) = M_n(0)\exp(-Kt)$ , wherein  $M_n(t)$  is the

number average molecular weight at time  $t$ ,  $M_n(0)$  is the number average molecular weight at  $t=0$ , and  $K$  is the hydrolytic degradation rate constant. Pitt, C.G., J. of Applied Polymer Science 26, 3779-3787 (1981); Pitt, C.G., Biomaterials 2, 215-220 (1981); Weir, N.A., Proceedings of the Institution of Mechanical Engineers, Part H: J. of Engineering in Medicine 218, 307-319 (2004); Weir, N.A., Part H: J. of Engineering in Medicine 218, 321-330 (2004). The assumptions inherent in the model are reasonable provided that the mass loss has not occurred, since mass loss would affect the concentrations of water and carboxylic end groups in the sample. The equation can also be written as:  $\ln [M_n(t)/M_n(0)] = Kt$ . Therefore, by representing data for  $M_n(t)/M_n(0)$  versus  $t$  on a log-linear plot, one may infer the hydrolytic degradation rate from the slope of the connecting points.

[0045] *In vitro* and *in vivo* degradation data has been generated for PLLA stents with different concentrations of LLA monomer to investigate its affect on the degradation behavior of a PLLA stent. The *in vivo* data was obtained using an animal model. Parameters and behavior that have been monitored include  $M_n$ , radial strength, appearance of cracks or fractures in stent struts (structural/mechanical integrity), and degradation time. In all studies, the stent is processed as described herein. The parameters of the stents are shown in Table 1 below. The stents included a coating over a scaffolding composed of poly(DL-lactide) and Everolimus.

Table 1. Summary stent parameters in degradation studies

Specification	Value
Backbone polymer (PLLA)	
Mw	180,000-200,000
Mn	90,000-100,000
Mass of stent (18mm length)	9.0 mg
Mass / unit length	0.5 mg /mm
Crystallinity	45 % (as measured by DSC)
Strut cross section	150 micron x 150 micron
Coating thickness	3 microns
Coating mass	308 $\mu$ g (1:1 polymer:Everolimus)
Coating polymer	
Mw	66,000
Mn	39,000
Blow molding:	
Percent radial expansion	400%
Percent axial elongation	20%
Laser machining	120 fs laser

[0046] The *in vitro* studies were performed in a phosphate buffered saline (PBS buffer) solution at 37 °C. The  $M_n$  of the stent was measured by GPC using polystyrene standards. The animal model for the *in vivo* studies was Yucatan mini swine.

[0047] In the *in vitro* study, the  $M_n$  dependence on time is plotted in the form of  $\ln[M_n(t)/M_n(0)]$  versus time to assess the predictive ability of the hydrolytic degradation model. The model is then used to assess the effect of LLA on the degradation of PLLA.

[0048] In the *in vitro* studies, the  $M_n$  as a function of time was also measured for PLLA stents having different concentrations of LLA monomer. In these studies, the LLA monomer was added to the PLLA resin in a manner described herein. FIG. 2 depicts a plot of  $\ln[M_n(t)/M_n(0)]$  versus time for this set for four groups of stents: nominal (0.05 wt % LLA), 0.2 wt% LLA, 0.55 wt% LLA, 1 wt% LLA, and 3.3 wt% LLA monomer in PLLA.

[0049] The data for each concentration is fitted with a straight line, the slope of which provides the rate constant,  $K$ , of the degradation model. The rate constant,  $K$ , for each concentration of LLA monomer is summarized in Table 2 and FIG. 3.

Table 2. Rate constant  $K$  for degradation model from *in vitro* data.

Stent Group: wt% LLA	$k \times 10^3 \text{ (days}^{-1}\text{)}$	$R^2$
Nominal	1.9	0.962



Stent Group: wt% LLA	$k$ ( $\times 10^3$ ) (days <sup>-1</sup> )	$R^2$
0.2	3.0	0.972
0.55	7.2	0.969
1	13.4	0.960
3.3	48.8	0.989

[0050] The coefficient of determination,  $R^2$ , is given for each group of data to assess the predictability of the linear degradation model. The closer  $R^2$  is to 1, the more reliable the predictive ability of the model. The data in Table 2 shows an unexpectedly dramatic effect of LLA monomer content on the degradation of the stent. For example, when the LLA concentration increases from near 0 to 0.55 wt%,  $k$  increases near three times and from near 0 to 1 wt%, the rate constant increases near six times. The differences in the change in the molecular weight with time as the LLA concentration increases is just as dramatic. Table 3 shows the percent drop in  $M_n$  and the  $M_n$  at time points based on the model predictions for 1 wt% LLA for the second set of data.

Table 3. Change in molecular weight with time for PLLA with 1 wt% PLLA

Days	Drop in $M_n$	$M_n$
20	23%	77 k
40	41%	59 k
60	55%	45 k
80	65%	35 k
120	80%	20 k

[0051] As indicated above, the loss of mechanical integrity starts before mass loss. In addition, the loss of radial strength occurs before or along with loss of mechanical integrity. At the entanglement molecular weight, about 17,000, the polymer no longer has mechanical properties and disintegrates under an applied load. The stent loses mechanical integrity well before the entanglement molecular weight.

[0052] As indicated above, the *in vitro* start of mass loss is expected to be an upper limit for *in vivo* degradation, that is, mass loss starts at an earlier time *in vivo*. In addition, the start of mechanical integrity loss and the loss of radial strength might also occur at an earlier time *in vivo* than *in vitro*. Table 4 shows *in vivo* and *in vitro* data for mass loss for a PLLA stent with no LLA monomer. The difference in the time that mass loss starts and the difference in the degree of loss is significant.

Table 4. Comparison of *in vitro* and *in vivo* mass loss for PLLA stent with no LLA monomer.

Time (months)	<i>In vitro</i> mass loss	<i>In vivo</i> Mass loss
9	0%	20%
12	0%	30%
18	-	35%
21	9%	-

[0053] For coronary and peripheral applications, it is believed that the mechanical integrity should remain intact for at least 2 to 4 months without severe fractures (e.g. breaking of struts) after implantation to allow incorporation of stent into vessel wall. Additionally, it is believed that radial strength should be maintained for at least about 1 month to prevent negative remodeling. The radial strength is expected to be lost prior to the mechanical integrity and the start of the loss of mechanical integrity is expected to start before mass loss. A prelude to the start of the loss of mechanical integrity corresponds to the formation of cracks in the stent. Therefore, based on this *in vitro* data, the LLA concentration should be less than 1 wt% for the stent to maintain radial strength and mechanical integrity for the desired times for coronary and peripheral applications.

[0054] In another set of *in vitro* studies, stent groups with near 0 wt%, 0.2 wt%, 0.55 wt%, 1 wt% and about 3 wt% of LLA in PLLA were studied and tracked over a four month period. In these studies, the radial strength and stent integrity were tracked. Table 5 summarizes the observed change in radial strength and mechanical integrity after radial strength testing for the different groups. As shown in Table 5, for near 0 wt%, 0.2 wt%, and 0.55 wt% LLA, the radial strength is maintained up to more than 4 months and there were no fractures observed up to more than 4 months. For 1 wt% LLA, the radial strength showed a consistent decrease

between about 1 ½ months to about 3 months. The drop in radial strength might occur sooner *in vivo*. Additionally, the significant fractures at only 42 days indicate an early loss of radial strength and mechanical integrity. These results indicate a stent with greater than 1 wt% LLA is very likely unsuitable for coronary or peripheral applications. The drop in radial strength and significant fractures in the stent with about 3 wt% LLA indicate that a PLLA stent with this concentration is totally unsuitable.

Table 5. Radial strength and mechanical integrity of PLLA stents with different LLA monomer content.

LLA content (wt%)	Radial strength	Mechanical integrity
0.05	maintained up to more than 4 months (126 days)	no fractures at up to more than 4 months (126 days)
0.2	maintained up to more than 4 months (126 days)	no fractures at up to more than 4 months (126 days)
0.55	maintained up to more than 4 months (126 days)	no fractures at up to more than 4 months (126 days)
1.0	consistent decrease between ~1 ½ months to about 3 months	stent segments in pieces observed at 42 days
~ 3	consistent decrease starting at about 2 weeks	stent segments in pieces observed at 14 days

**[0055]** Preclinical *in vivo* (animal) results for stent groups with a 0 wt%, 0.1 wt%, 0.4 wt % LLA, ca. 0.6 wt% LLA, 1 wt% LLA, and 3.8 wt% LLA have been obtained for up to 28 days after implantation. For stents with 0.4 wt% LLA and ca. 0.6% there were no fractures observed at 28 days after implantation. For stents with 1 wt% LLA, fractures were observed at 28 days after implantation. For stents with 3.8 wt% LLA, there were significant fractures at only 7 days and the stent broke into pieces after 28 days.

**[0056]** It has been observed by the inventor that forming a PLLA tube intended to have between 0.05 - 0.5 wt% LLA by mechanical blending of the requisite amount of LLA in PLLA fails to result in tubes with uniform blending of the LLA. Large variations in LLA concentration between stents formed from tubes in this manner were observed.

**[0057]** Two methods are provided that result in uniform blending with consistent concentration in LLA monomer in different tubes and stents fabricated therefrom. The first method includes making a master batch of PLLA and LLA mixture with concentrations of LLA larger than the target concentration. The master batch is made by dissolving LLA and PLLA in a solvent such as chloroform. The chloroform is evaporated to form the master batch with is a uniform mixture of PLLA and LLA. The master batch is then mixed by melt processing, such as in an extruder, with a sufficient amount of PLLA to obtain the target LLA concentration. The method is illustrated by the following example:

Step 1: Dissolve 2g LLA monomer and 8 g PLLA in 400 ml chloroform

Step 2: Evaporate chloroform to form uniform mixture of PLLA and LLA with 25 wt% LLA.

Step 3: Blend 25 wt% LLA mixture in extruder with 4 kg of PLLA to obtain 0.5 wt% LLA in PLLA.

The second method of preparing a uniform mixture of LLA in PLLA includes dissolving LLA in a solvent such as chloroform to form a solution and spraying the solution on PLLA pellets. The solvent is removed leaving the LLA deposited on the PLLA pellets. The PLLA pellets are melt processed, in an extruder, for example, to form tubes with the target concentration of LLA in PLLA. The method is illustrated by the following example:

Step 1: Dissolve 0.5 g LLA in 100 ml anhydrous methanol to form solution.

Step 2: Spray solution onto 1 kg of PLLA pellets and stir.

Step 3: Place pellets in vacuum oven to remove solvent.

Step 4: Place pellets in extruder and form tube with 0.5 wt% of LLA.

## REFERENCES CITED IN THE DESCRIPTION

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**BIOLOGISK NEDBRYDELIG STENT MED JUSTERBAR NEDBRYDNINGSHASTIGHED****PATENTKRAV**

1. Stent til behandling af en sygdomsramt sektion af et blodkar, hvilken stent omfatter et polymerstillads omfattende poly(L-lactid) og mellem 0,05 til 0,5 vægt-% L-lactidmonomer blandet,  
5 dispergeret eller opløst i poly(L-lactidet), hvor krystalliseringsgraden for poly(L-lactidet) er mellem 20-50, og hvor antalsmiddelmolekylvægten af poly(L-lactidet) er mellem 60.000 og 300.000, i forhold til polystyrenstandarder.
2. Stent ifølge krav 1, hvor stilladset omfatter mere end 95 vægt-% poly(L-lactid).
3. Stent ifølge krav 1, hvor stilladset består af et mønster af stivere, hvilket mønster indbefatter en  
10 flerhed af cylindriske ringe, der er forbundet ved forbindende stivere.
4. Stent ifølge krav 3, hvor stiverne har et rektangulært tværsnit, hvilket tværsnitsareal er mellem 20.000 og 25.000  $\mu\text{m}^2$ .
5. Stent ifølge krav 1, hvor stilladset har en polymerkædeorientering, der er induceret af radial ekspansion af et rør mellem 200-500 % og dannelse af stenten deraf.
- 15 6. Stent ifølge krav 1, hvor L-lactidet er i form af partikler med en størrelse mellem 100 og 1000 nm.

# DRAWINGS

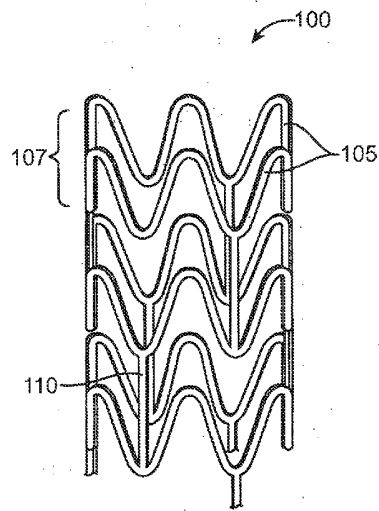


FIG. 1

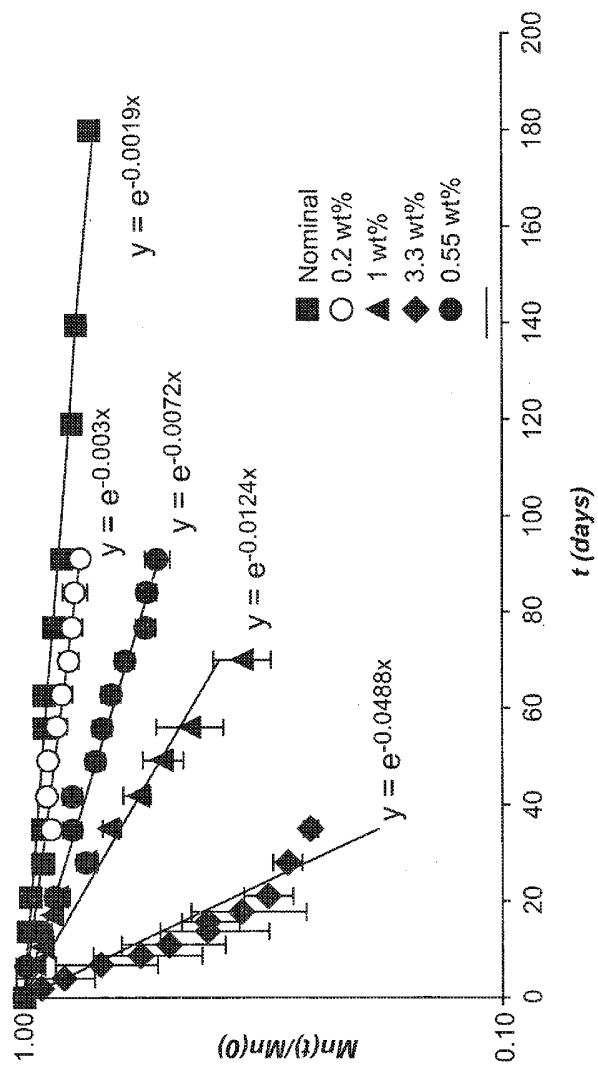


FIG. 2

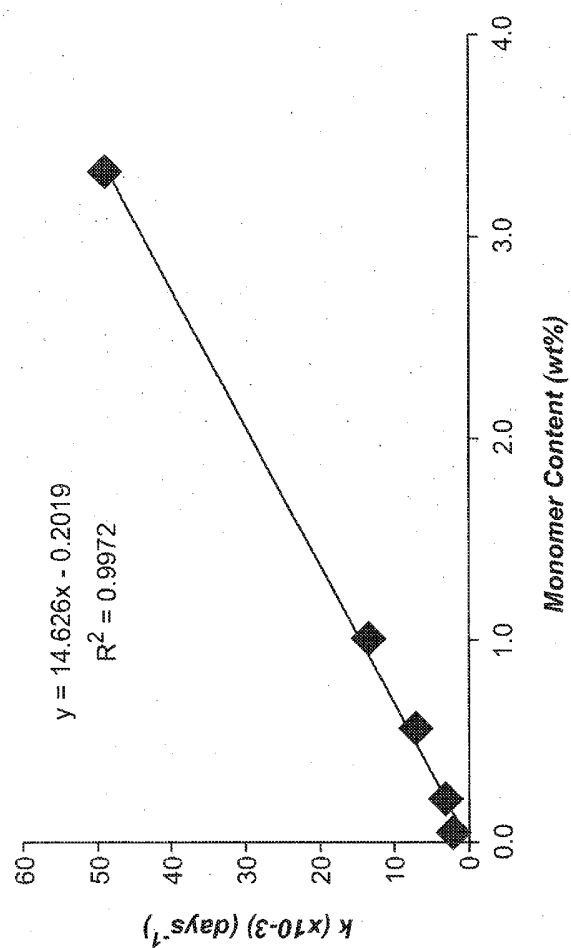


FIG. 3