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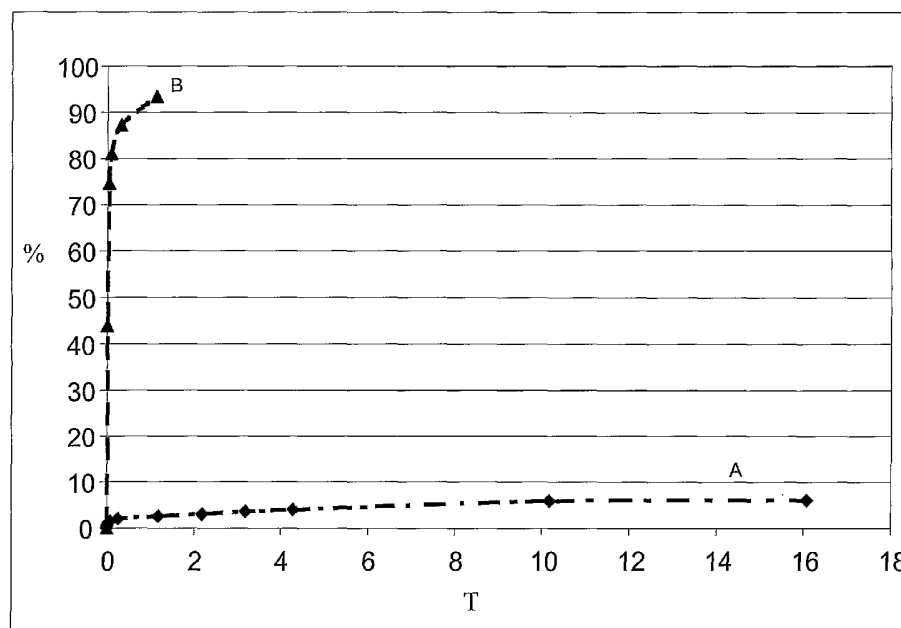
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(54) Title: BIODEGRADABLE COATING COMPOSITIONS COMPRISING BLENDS



(57) Abstract: The invention provides devices for treatment of a patient, wherein at least a portion of the device is provided with a biodegradable coating composed of a blend of bioactive agent and at least two biodegradable polymers or copolymers. The invention further provides methods of treatment utilizing the devices.

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BIODEGRADABLE COATING COMPOSITIONS COMPRISING BLENDS

Cross-Reference to Related Applications

The present non-provisional Application claims the benefit of commonly owned
5 provisional Application having serial number 60/641,533, filed on January 5, 2005, and
entitled BIODEGRADABLE COATING COMPOSITIONS COMPRISING BLENDS.

Field Of the Invention

The invention relates to medical devices having a biodegradable component that are
useful for effectively treating a treatment site within a patient's body, for example, treatment
10 of vascular structures and other areas within the body. More specifically, the invention
relates to biodegradable coating compositions for drug delivery in association with
implantable medical devices.

Background of the Invention

Tubular organs and structures such as blood vessels are subject to narrowing or
15 occlusion of the lumen. Such narrowing or occlusion can be caused by a variety of
traumatic or organic disorders, and symptoms can range from mild irritation and discomfort
to paralysis and death. Treatment is typically site-specific and varies with the nature and
extent of the occlusion.

Life threatening stenoses are most commonly associated with the cardiovascular
20 system and are often treated using percutaneous transluminal coronary angioplasty (PTCA).
This process improves the narrowed portion of the lumen by expanding the vessel's
diameter at the blockage site using a balloon catheter. However, three to six months after
PTCA, approximately 30% to 40% of patients experience restenosis. Restenosis is thought
to be initiated by injury to the arterial wall during PTCA. Restenosis primarily results from
25 vascular smooth muscle cell proliferation and extracellular matrix secretion at the injured

site. Restenosis is also a major problem in non-coronary artery disease including the carotid, femoral, iliac, and renal arteries.

Stenosis of non-vascular tubular structures is often caused by inflammation, neoplasm and/or benign intimal hyperplasia. In the case of esophageal and intestinal strictures, the obstruction can be surgically removed and the lumen repaired by anastomosis. The smaller transluminal spaces associated with ducts and vessels can also be repaired in this fashion; however, restenosis caused by intimal hyperplasia is common. Furthermore, dehiscence is also frequently associated with anastomosis requiring additional surgery, which can result in increased tissue damage, inflammation, and scar tissue development leading to restenosis.

Much recent attention has been directed to drug eluting stents (DES) that present or release bioactive agent into their surroundings (for example, luminal walls or coronary arteries). Generally speaking, bioactive agent can be coupled to the surface of a medical device by surface modification, embedded and released from within polymer materials (matrix-type), or surrounded by and released through a carrier (reservoir-type). The polymer materials in such applications should optimally act as a biologically inert barrier and not induce further inflammation within the body. However, the molecular weight, porosity of the polymer, and the thickness of the polymer coating can contribute to adverse reactions to the medical device.

An ongoing technical challenge with present drug eluting coatings applied to devices such as stents is achieving a therapeutic concentration of a bioactive agent locally at a target site for a prescribed time within the body without producing unwanted systemic side effects. Implantation of vascular stents is a prime example of a situation where local therapy is needed utilizing bioactive agents that can also produce unwanted systemic side effects. Because the stent is placed within a flowing blood stream, during placement and upon implantation, potential unwanted systemic effects may result from undesirable

quantities (for example, undesirably high quantities) of the therapeutic substance entering the blood stream. Further, if quantities of therapeutic substance are released into the blood stream as part of a "burst" effect, less of the therapeutic substance is available for actual local treatment once the stent is emplaced, resulting in potential inadequate local dosing.

5 Some recent work has been done to utilize degradable materials in association with stents, as well as DES. Degradable devices and degradable coatings provided on devices typically have bioactive agent physically immobilized in the polymer. The bioactive agent can be dissolved and/or dispersed throughout the polymeric material. The degradable polymeric material is often hydrolytically degraded over time through hydrolysis of labile
10 bonds, allowing the polymer to erode into the fluid, releasing the active agent into the fluid. Generally speaking, hydrophilic polymers typically have a faster rate of erosion relative to hydrophobic polymers. Hydrophobic polymers are believed to have almost purely surface diffusion of water, resulting in erosion from the surface inwards. Hydrophilic polymers are believed to allow water to penetrate the surface of the polymer, allowing hydrolysis of labile
15 bonds beneath the surface, which can lead to homogeneous or bulk erosion of polymer.

 The goal of sustained-release systems is to maintain bioactive agent levels within a therapeutic range and ideally a constant and predictable level. In order to achieve relatively constant levels, bioactive agents should be released from a delivery system at a rate that does not change with time (so called zero-order release). Preferably, the initial dose of a
20 bioactive agent is the therapeutic dose that is maintained by the delivery system. In many systems, however, the bioactive agent release is proportional to time (zero order release) or the square root of time (Fickian release).

 In nondegradable polymeric matrix systems for bioactive agent delivery, bioactive agent is dispersed throughout a matrix and is released as it dissolves and diffuses through
25 the matrix. A bioactive agent is released from the outer surface of the matrix first, this layer becomes depleted, and the bioactive agent that is released from further within the core of the

device must then diffuse through the depleted matrix. The net result is that the release rate slows down over time.

When the polymeric matrix systems are degradable, release of the bioactive agent can occur by diffusion (as discussed for nondegradable polymeric matrix systems), and also
5 via degradation of the polymer. The lifetime of a biodegradable polymer *in vivo* can depend upon its molecular weight, crystallinity, biostability, and the degree of crosslinking. In general, the greater the molecular weight, the higher the degree of crystallinity, and the greater the biostability, the slower biodegradation will be. Accordingly, degradation times can vary widely, for example, from less than one day to several months. Thus, release
10 kinetics become even more complex from biodegradable polymeric matrix systems. As a result of the multiple mechanisms of release of bioactive agent from a biodegradable polymeric matrix, zero-order release from these types of systems is very difficult to achieve.

Summary of the Invention

Generally, the invention provides implantable medical devices including
15 biodegradable compositions as a coating on a surface of the device. In some aspects, the polymeric formulations of the invention biodegrade within a period that is acceptable for the desired application. In certain aspects, such as *in vivo* therapy, such degradation occurs in a period usually less than about one year, or less than about six months, three months, one month, fifteen days, five days, three days, or even one day, on exposure to a physiological
20 solution with a pH between 6 and 8 having a temperature in the range of about 25° to about 37°C. In some embodiments, the polymeric formulation degrades in a period in the range of about an hour to several weeks, depending upon the desired application.

In its article aspects, the invention provides a device having a surface and a coating disposed on the surface, the coating comprising bioactive agent and a blend of a first
25 biodegradable polymer and a second biodegradable polymer. The first biodegradable polymer is preferably a polyether ester copolymer, such as poly(ethylene glycol)

terephthalate/polybutylene terephthalate (PEGT/PBT). In some embodiments, the device is a stent, and in particular can be a vascular stent.

According to the invention, the biodegradable compositions are composed of a blend of two or more biodegradable polymers. The first biodegradable polymer has a
5 different bioactive agent release rate as compared to the second biodegradable polymer (and subsequent biodegradable polymers, when more than two polymers comprise the blend). In some embodiments, the second biodegradable polymer has a slower bioactive agent release rate than the first biodegradable polymer.

In some article aspects, the invention provides implantable medical articles having a
10 bioactive agent releasing coating, the coating comprising a blend of (a) first biodegradable polymer that is a copolymer of polyalkylene glycol terephthalate and an aromatic polyester; (b) a second biodegradable polymer; and (c) bioactive agent, wherein the second biodegradable polymer is selected to have a slower bioactive agent release rate relative to the first biodegradable polymer.

15 In addition to polyether ester copolymers, other polymers containing ester linkages that are suitable first biodegradable polymers include terephthalate esters with phosphorus-containing linkages, and segmented copolymers with differing ester linkages. Other suitable first biodegradable polymers include polycarbonate-containing random copolymers. The second biodegradable polymer is selected to modify the bioactive agent release rate from the
20 biodegradable composition, to achieve a controlled release rate.

The first biodegradable polymer and second biodegradable polymer are provided as a blend, thereby forming a bioactive agent releasing coating. In some aspects, the blend comprises a miscible blend, as discussed herein. Typically, the blended composition includes a lower amount of the first polymer (polyether ester copolymer or other first
25 polymer) relative to the second polymer. In some aspects, 50% or less of the coating composition is composed of the first polymer. In some aspects, the first polymer is present

in an amount of about 50% by weight or less, or about 40% or less, or about 30% or less, or about 20% or less, or about 10% or less, based upon total weight of the coating composition. In some aspects, the first polymer is present in an amount in the range of about 1% to about 35% by weight, based upon total weight of the coating composition.

5 In some aspects, the biodegradable composition comprises a coating on a surface, such as a surface of an implantable device. A “coating” as described herein can include one or more “coated layers,” each coated layer including one or more coating components. One or more of the coated layers is composed of a blended biodegradable composition. Bioactive agent can be present in one or more of the coated layers.

10 When more than one coated layer is applied to the surface of a device, it is typically applied successively. For example, a coating is typically formed by dipping, spraying, or brushing a coating material on a device to form a layer, and then drying the coated layer. The process can be repeated to provide a coating having multiple coated layers, wherein at least one layer includes a bioactive agent. Typically (but not always), at least the coated
15 layer located nearest the device surface includes bioactive agent. In some aspects, more than two coated layers can be present. Such other layers can be the same or different than the first coated layer and/or second coated layer. The suitability of the coating for use with a particular medical article, and in turn, the suitability of the application technique, can be evaluated by those skilled in the art, given the present description.

20 In its method aspects, the invention provides methods of making a device for controlled release of bioactive agent, the method comprising steps of providing a device having a surface, blending a first biodegradable polymer and second biodegradable polymer to form a blended biodegradable polymer composition, providing bioactive agent to the blended biodegradable polymer composition to form a blended bioactive agent composition,
25 and providing the blended bioactive agent composition to the surface. The first biodegradable polymer is preferably a polyether ester copolymer, such as poly(ethylene

glycol) terephthalate/polybutylene terephthalate (PEGT/PBT), or can be any of the suitable first polymers described herein. The second biodegradable polymer is selected to control release of the bioactive agent from the blended bioactive agent composition.

In further aspects, the invention provides methods for delivery of bioactive agent to a patient in a controlled manner, the method comprising steps of providing a device to a patient, the device having a surface and a biodegradable coating composition disposed on the surface, the biodegradable coating composition comprising bioactive agent and a blended biodegradable polymer composition. In some aspects, the method includes a step of maintaining the device in the patient for a selected period of time, during which time the bioactive agent is released from the coating composition in a controlled and predictable manner.

In a more specific aspect, the invention provides devices and methods for providing treatment (for example, of vascular structures), wherein the devices include at least a component that is biodegradable. In preferred aspects, any portions of the device that remain in the body (are not degraded) do not cause significant adverse foreign body response.

Preferred compositions and methods according to the invention provide the ability to control the release rate of bioactive agent from the device surface over time. The inventive biodegradable compositions are composed of a blend of a first polymer and second polymer, wherein the bioactive agent release rates of the first and second polymer are different. In some aspects, the bioactive agent release rate can be controlled by selecting the second polymer and/or by adjusting the relative amounts of the first polymer and second polymer to achieve the desired release profile of the bioactive agent.

In preferred aspects, the inventive biodegradable compositions are selected to provide a controlled release profile of bioactive agent from the biodegradable coatings. The release profile is the cumulative mass of bioactive agent released versus time. The time

profile of the release of bioactive agent, including immediate release and subsequent, sustained release can be predictably controlled utilizing the inventive compositions and methods. In some aspects of the invention, the initial release of bioactive agent is controlled, thereby permitting more of the bioactive agent to remain available at later times
5 for a more extended release duration. The shape of the release profile after an initial release can be controlled to be linear, logarithmic, or some more complex shape, depending upon the composition of the coated layers of the coating and bioactive agent(s) in the coating. In some embodiments, additives can be included in the biodegradable composition to further control the release rate. In preferred aspects, the inventive biodegradable compositions
10 maintain bioactive agent levels within a therapeutic range and ideally a relatively constant level.

Surprisingly, some embodiments of the invention provide devices and methods of reproducibly releasing bioactive agent in a linear manner over extended periods of time. As described herein, *in vitro* elution assays of preferred embodiments of the invention show
15 surprisingly controllable release of bioactive agent over time. In preferred embodiments, coating compositions having varying formulations (in terms of polymer ratios) can provide substantially linear release rates of bioactive agent. Based upon the *in vitro* data presented herein, it is expected that *in vivo* release rates will provide reproducible release rates in a linear manner over an extended period of time. Thus the invention can provide controlled
20 release of bioactive agent to an implantation site that can be adjusted to accommodate desired treatment duration and dosage. Because the invention provides local delivery of one or more bioactive agents to an implantation site, the invention also preferably avoids toxic levels of bioactive agents that can be required during systemic treatment.

The inventive biodegradable compositions can find particular application when the
25 bioactive agent comprises a relatively small molecule. In preferred aspects, the inventive concepts provide methods to allow controlled release of small molecules achievable in a

therapeutically effective manner from biodegradable coatings provided on implantable device surfaces. Small molecules are typically released from biodegradable polymeric compositions via two routes, namely, diffusion through the polymeric material and degradation of the polymer material. Thus, it can be particularly difficult to control release of such molecules, especially if one wishes to avoid or minimize a relatively fast “burst” release during the initial time period after implantation of the device. The inventive biodegradable compositions can provide improved control over release of such small molecules, for example, by modulating the initial release of the bioactive agent from the biodegradable composition. Typically, small molecule bioactive agents have a molecular weight that in general is less than about 1500.

Some illustrative bioactive agents include smaller molecules having anti-proliferative effects (such as actinomycin D, paclitaxel, taxane, and the like), anti-inflammatory agents (such as dexamethasone, prednisolone, tranilast, and the like), immunosuppressive agents (such as cyclosporine, CD-34 antibody, everolimus, mycophenolic acid, sirolimus, tacrolimus, and the like), smaller molecule antibiotics, and the like. Suitable bioactive agents have been described, for example, a comprehensive listing of bioactive agents and therapeutic compounds can be found in The Merck Index, Thirteenth Edition, Merck & Co. (2001). One of skill in the art, using the guidance of the present description, can readily select bioactive agents that are suitable to be eluted from the polymeric matrices of the invention.

In use, an implantable medical device is provided with a biodegradable coating and positioned within the body at a treatment site. In one such application, a stent is placed into a body vessel after a procedure, such as angioplasty. The stent is left in position, and the biodegradable coating is allowed to degrade. Upon placement of the stent, and thus exposure of the biodegradable coating to physiological fluids, bioactive agent is released from the stent. Typically, an initial release of the bioactive agent is observed, and over time

a sustained release of the bioactive agent is observed. As the biodegradable coating degrades, bioactive agent continues to be released in a controlled manner, thereby providing a therapeutically effective amount of the bioactive agent over a treatment course to the treatment site.

5 These and other aspects and advantages will now be described in more detail.

Brief Description of the Drawings

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several aspects of the invention and together with the description of the preferred embodiments, serve to explain the principles of the invention. A brief
10 description of the drawings is as follows:

FIG. 1 is a graph illustrating elution profiles for two unblended polymers, wherein time (T, in days) is represented on the X axis, and percent bioactive agent eluted (%) is represented on the Y axis.

15 FIG. 2 is a graph illustrating elution profiles for blended coating compositions in accordance with some aspects of the invention, wherein time (T, in days) is represented on the X axis, and percent bioactive agent eluted (%) is represented on the Y axis.

FIG. 3 is a graph illustrating elution profiles for blended coating compositions in accordance with some aspects of the invention, wherein time (T, in days) is represented on the X axis, and percent bioactive agent eluted (%) is represented on the Y axis.

20 FIG. 4 is a graph illustrating elution profiles for blended coating compositions in accordance with some aspects of the invention, wherein time (T, in days) is represented on the X axis, and percent bioactive agent eluted (%) is represented on the Y axis.

FIG. 5 is an optical image of a surface of a coated device in accordance with some aspects of the invention, shown at 100X magnification.

25 FIG. 6 is an optical image of a surface of a coated device in accordance with some aspects of the invention, shown at 100X magnification.

FIG. 7 is an optical image of a surface of a coated device in accordance with some aspects of the invention, shown at 100X magnification.

FIG. 8 is a Scanning Electron Microscope (SEM) image of a surface of a coated device in accordance with some aspects of the invention.

5 FIG. 9 is a Scanning Electron Microscope (SEM) image of a surface of a coated device in accordance with some aspects of the invention.

FIG. 10 is a Scanning Electron Microscope (SEM) image of a surface of a coated device in accordance with some aspects of the invention.

10 FIG. 11 is an optical image of a surface of a coated device in accordance with some aspects of the invention, shown at 100X magnification.

FIG. 12 is an optical image of a surface of a coated device in accordance with some aspects of the invention, shown at 100X magnification.

FIG. 13 is an optical image of a surface of a coated device in accordance with some aspects of the invention, shown at 100X magnification.

15 FIG. 14 is an SEM image of a surface of a coated device in accordance with some aspects of the invention.

FIG. 15 is an SEM image of a surface of a coated device in accordance with some aspects of the invention.

20 FIG. 16 is an SEM image of a surface of a coated device in accordance with some aspects of the invention.

Detailed Description of the Invention

The embodiments of the present invention described below are not intended to be exhaustive or to limit the invention to the precise forms disclosed in the following detailed description. Rather, the embodiments are chosen and described so that others skilled in the art can appreciate and understand the principles and practices of the present invention.

25

The invention is directed to medical devices provided with a biodegradable material in the form of a coating. At least a portion of the device is coated with the biodegradable material, and this portion is broken down gradually by the body after implantation. In some embodiments, the biodegradable composition can be bioabsorbable in addition to being biodegradable. According to these embodiments, the biodegradable composition is resorbed by the body. It is not required that the component is resorbed by the body; in some embodiments, the biodegradable composition is broken down into a plurality of portions that are not completely resorbed by the body.

The present invention is directed to methods and apparatuses for effectively treating a treatment site within a patient's body, and in particular for treating vascular sites.

According to preferred embodiments of the invention, stents are provided that can provide treatment to a site within the body for a desired period of time, after which at least a portion of the stent (such as the coating) degrades. The inventive methods and apparatuses can be utilized to deliver bioactive agent to a treatment site in a controlled manner. Such methods and apparatuses in accordance with the present invention can advantageously be used to provide flexibility in treatment duration, as well as type of bioactive agent delivered to the treatment site. In particular, the present invention has been developed for controllably providing one or more bioactive agents to a treatment site within the body for a desired treatment course.

As used herein, "controlled release" refers to release of a compound (for example, a bioactive agent) into a patient's body at a desired dosage (including dosage rate and total dosage) and duration of treatment.

The term "implantation site" refers to the site within a patient's body at which the implantable device is placed according to the invention. In turn, a "treatment site" includes the implantation site as well as the area of the body that is to receive treatment directly or indirectly from a device component. For example, bioactive agent can migrate from the

implantation site to areas surrounding the device itself, thereby treating a larger area than simply the implantation site.

Bioactive agent is released from the inventive coatings over time, and this relationship can be plotted to establish a release profile (cumulative mass of bioactive agent released versus time). Typically, the bioactive agent release profile can be considered to include an initial release of the bioactive agent, and a release of the bioactive agent over time, and the distinction between these two can often be simply the amount of time. The initial release is that amount of bioactive agent released shortly after the device is implanted, and the release of bioactive agent over time includes a longer period of time (for example, the lifespan of the biodegradable composition).

In some cases, the initial release can be characterized as a "burst" release. For coatings that provide a "burst release" of bioactive agent, an initial release of a significant amount of bioactive agent is observed within a relatively short period of time after an implantable device is provided within a patient. A typical burst release is a much higher release in a relatively short amount of time (for example, more than 30% of the amount of bioactive agent contained in the coating within the first 24 hours after implantation). In contrast, coatings can provide substantially linear release of bioactive agent, wherein the initial release of bioactive agent does not comprise a significantly different slope or shape than the overall release profile. Put another way, a burst release can be characterized as an initial release that differs in magnitude of bioactive agent released as compared to release of bioactive agent over time (that is, a significant amount is released during the initial period).

The significance of a burst release can also be considered in relation to the particular polymeric material that contains the bioactive agent. For example, for a biodegradable polymer having a half-weight degradation time of four weeks, a significant burst release can be considered to be more than about 30% of the bioactive agent contained in the coating that is released within the first 24-hour period. For a biodegradable polymer

having a half-weight degradation time of more than four weeks, a longer burst time period can be considered significant for the same amount of bioactive agent. For example, the half-weight degradation time of poly(D,L-lactide) (PLA) is approximately 155 days (depending upon molecular weight of the polymer), compared to 30 days for poly(D,L-lactide-co-glycolide) (PLGA). Thus, a longer time period would be considered therapeutically relevant for the burst release from PLA compared to PLGA.

In accordance with some aspects of the invention, the shape of the bioactive agent release curve can be modulated by controlling one or more characteristics of the coating, such as the selection of the second polymer, and the relative amounts of first polymer and second polymer in the blended composition. In accordance with the invention, the time profile of the release of bioactive agent can be modulated to provide any desired shape, including immediate release where the drug elutes all at once (much like a step function) to an extremely slow, linear (i.e., zero order) release, where the drug is evenly released over many months or years. Depending on the drug and the condition being treated, a variety of release profiles can be achieved. The objective of creating coatings with the inventive blended coatings is to be able to attain the broad range of release profiles that lie between a step function and a low-slope, zero-order release. Preferably, the relative amount of each polymer of the biodegradable composition is selected to provide the desired release profile. In addition, or alternatively, the second polymer (and additional polymers, if included) can be selected to provide the desired release profile. By controlling the release profiles as described herein, significant improvements can be made to the efficacy of treatment with bioactive agent.

The desired release profile of the bioactive agent can depend upon such factors as the particular bioactive agent selected, the number of individual bioactive agents to be provided to the implantation site, the therapeutic effect to be achieved, the duration of the implant in the body, and other factors known to those skilled in the art.

The ability to provide controlled release of a bioactive agent at an implantation site can provide many advantages. For example, the controlled delivery device can be maintained at an implantation site for any desired amount of time, and the release kinetics of the bioactive agent can be adjusted to deliver the total amount of bioactive agent, at the
5 desired rate, to achieve a desired therapeutic effect. In some embodiments, the ability to provide controlled release of bioactive agent at the implantation site allows implantation of only one device, which can be maintained in place until the desired therapeutic effect is achieved, without need to provide a new supply of bioactive agent (systemically or locally).

In some embodiments, when PEGT/PBT copolymers are utilized as the first
10 polymer, the second polymer can be selected to have particular release rates that can modulate the relatively fast release rate of the PEGT/PBT copolymer. The resulting release rate of the blended biodegradable coating is thus an intermediate between the relatively fast PEGT/PBT release rate, and the relatively slower release rate of the second (and optionally additional) polymer(s). In addition, or alternatively, the relative amount of first polymer to
15 second polymer can be selected to provide an initial release phase that is less than a burst release. For example, a blended composition composed of PEGT/PBT as first polymer and poly(L-lactide) (PLLA) as second polymer, wherein the PEGT/PBT is present in a larger weight percentage than PLLA, can provide a relatively faster release rate. If it is desired to provide a relatively slower release rate, the amount of PLLA can be increased, and the
20 amount of PEGT/PBT can be decreased. By controlling the initial release phase as described herein, significant improvements can be made to the efficacy of treatment with bioactive agent.

Surprisingly, it has been discovered that small changes in the amount of first polymer present in a blended coating composition, in accordance with principles of the
25 invention, can have a large affect on elution of bioactive agent from the inventive coatings. For example, significant differences can be observed in bioactive agent release from

coatings containing 5% polyetherester copolymer, versus coatings containing 50% polyetherester copolymer as first polymer. In some aspects, particularly dramatic differences in bioactive agent release can be seen in coatings containing polyetherester copolymer in an amount in the range of about 5% to about 10%. Such differences in bioactive agent release can be observed in initial release phase and over time subsequent to the initial release phase. Some illustrative release profiles are shown in the Examples herein.

The inventive blended coatings described herein can be designed to control (such as, for example, by limiting or even eliminating) the initial burst of bioactive agent from the coating. The bioactive agent still remaining in the coating after the burst release is then released to the site of action over a longer time period. The shape of the release profile (percentage of bioactive agent released versus time) after the initial release phase can be controlled to be linear or logarithmic or some more complex shape, again depending upon the composition of the blended coating and bioactive agent in the coating composition.

As used herein, a treatment course is a period of time during which bioactive agent is delivered to a patient. The duration of the treatment course is typically determined by the physician, based upon such factors as condition to be treated, the age and condition of the patient, the normal reaction time of the body to the procedure necessitating stent implantation (such as angioplasty), and the like. Typically, a treatment course will span from hours to days to weeks or even months. For example, a typical treatment course for minimizing risk of restenosis upon implantation of a stent is approximately 4 or more weeks.

The *in vivo* release of a bioactive agent can be approximated by observing the *in vitro* release of the bioactive agent. For example, an implantable device can be fabricated to include a biodegradable coating containing a bioactive agent. The coated implantable device can then be placed in an appropriate solution (for example, a buffer solution such as

phosphate buffered saline or Tween acetate buffer) for a period of time. During incubation of the device, the solution can be periodically monitored to determine the *in vitro* release rate of the bioactive agent into the solution. The stent is removed from the solution and placed in fresh buffer solution in a new vial at periodic sampling times. Concentration of bioactive agent at each sampling time can be determined in the spent buffer by spectroscopy using the characteristic wavelength for each bioactive agent. The concentration can be converted to a mass of bioactive agent released from the coating using molar absorptivities. The cumulative mass of the released bioactive agent can be calculated by adding the individual sample mass after each removal. The release profile can be obtained by plotting the cumulative mass of released bioactive agent as a function of time. From this determined *in vitro* release rate, the *in vivo* release rate can be approximated using known techniques.

According to the invention, implantable devices include a biodegradable composition that is composed of a blend of a first polymer and a second polymer. The biodegradable composition further includes bioactive agent for treatment of a treatment site. In preferred aspects, the invention provides devices and methods for providing controlled release of the bioactive agent to the treatment site.

In some aspects, the inventive biodegradable compositions can exhibit controlled release characteristics, in contrast to a bolus type administration (which includes an initial burst release of bioactive agent) in which a substantial amount of the bioactive agent is made biologically available at one time. For example, in some embodiments, upon contact with body fluids including blood, spinal fluid, lymph, or the like, the biodegradable compositions (formulated as provided herein) can permit a desired amount of initial release of bioactive agent, and subsequently provide a sustained, predictable delivery of the bioactive agent over time. This release can result in prolonged delivery of therapeutically effective amounts of any incorporated bioactive agent. Sustained release will vary in certain embodiments as described in more detail herein.

The phrase "therapeutically effective amount" is an art-recognized term. In some aspects, the term refers to an amount of the bioactive agent that, when incorporated into a biodegradable composition of the invention, produces some desired effect at a reasonable benefit/risk ratio applicable to any medical treatment. In some aspects, the term refers to that amount necessary or sufficient to eliminate or reduce risk of restenosis. The therapeutically effective amount can vary depending upon such factors as the condition being treated, the particular bioactive agent(s) being administered, the size of the patient, the severity of the condition, and the like. In preferred aspects, the therapeutically effective amount takes into account the amount of bioactive agent released from the biodegradable composition during any selected time period, particularly the time period during implantation and immediately after the device is emplaced (the initial release). Thus, the therapeutically effective amount also applies to the initial release of bioactive agent from the biodegradable composition. By controlling the initial release from the biodegradable composition, preferred embodiments can reduce or eliminate potentially undesirably high amounts of drug release during early stages after implantation. One of ordinary skill in the art can empirically determine the effective amount of a particular bioactive agent without necessitating undue experimentation.

Preferred aspects of the invention can thus provide one or more advantages, including the ability to provide sustained bioactive agent delivery that can maintain the bioactive agent concentration within a therapeutic window for a prolonged period of time and improve bioactive agent efficacy. Local delivery can reduce drug dosage, toxicity effects, and other side effects that are typically associated with administration of therapeutics.

According to the present invention, a device has been developed that can be used to treat any implantation site within the body in which it is desirable to provide a device having a coating that degrades (at least in part) during use. In some embodiments, the device is

preferably used to treat an implantation site within the body in which it is desirable to restore and maintain patency of the implantation site while permitting function of the implantation site. For example, in vascular applications, the device can restore and maintain patency of the vascular site treated with the device, thus permitting continued blood flow through the treatment site. The inventive device further provides controlled release of one or more bioactive agents. According to this aspect of the invention, the device can provide controlled release of the bioactive agent to a treatment site within the body. As described herein, controlled release at the treatment site can mean control both in dosage rate and total dosage.

10 To facilitate the discussion of the invention, use of the invention to treat a vascular site will be addressed. Vascular treatment is selected because the features of the invention, particularly relating to controllable drug delivery capabilities can be clearly presented. Further, the ability to provide controlled and predictable delivery of a bioactive agent that can provide superior qualities while reducing risks to the patient can be a significant advance in the field. Emphasis is given to treatment of a vascular site with a stent; however, other devices such as vascular filters (for example, emboli filters) can also utilize the concepts of the invention.

20 It is understood that the device and methods disclosed are applicable to any treatment needs, for example, ophthalmic devices, orthopedic appliances or bone cement for repairing injuries to bone or connective tissue (for example, bone screws and other fixative devices that can be utilized to maintain relative position and stability to bones during a healing process, including, but not limited to, connective devices such as ties, tethers, and the like), coatings for degradable or nondegradable fabrics or paper substrates, scaffolds for tissue engineering, and the like.

25 In some embodiments, the biodegradable composition can include additional layers, for example, between the first and second layers, and/or at the outermost layer of the coated

device (thus the tissue-contacting surface), while in other embodiments, the biodegradable compositions are composed of the layers described in detail herein.

In some aspects, the inventive biodegradable compositions are utilized to provide a coating composed of a blend of a first biodegradable polymer, a second biodegradable
5 polymer, and a bioactive agent. The first biodegradable polymer is preferably a polyether ester copolymer, such as PEGT/PBT. Other polymers containing ester linkages that are suitable first biodegradable polymers include terephthalate esters with phosphorus-containing linkages, and segmented copolymers with differing ester linkages. In still further aspects, the first biodegradable polymer can comprise a polycarbonate-containing random
10 copolymer. These aspects will now be described in more detail.

As used herein, the term "aliphatic" refers to a linear, branched, and/or cyclic alkane, alkene, or alkyne. Preferred aliphatic groups in polymeric materials that include phosphoester linkages are linear or branched alkanes having 1 to 10 carbon atoms, or linear alkane groups having 1 to 7 carbon atoms.

15 As used herein, the term "aromatic" refers to an unsaturated cyclic carbon-containing compound with $4n+2$ π electrons.

As used herein, the term "heterocyclic" refers to a saturated or unsaturated ring compound having one or more atoms other than carbon in the ring, for example, nitrogen, oxygen or sulfur.

20 Generally speaking, the polyetherester copolymers are amphiphilic block copolymers that include hydrophilic (for example, a polyalkylene glycol, such as polyethylene glycol) and hydrophobic blocks (for example, polyethylene terephthalate).

In one embodiment, the polyetherester copolymer comprises a first component that is a polyalkylene glycol, and a second component, which is a polyester, formed as the
25 reaction product from an alkylene glycol having from 2 to 8 carbon atoms and a dicarboxylic acid. The polyalkylene glycol, in one embodiment, is selected from the group

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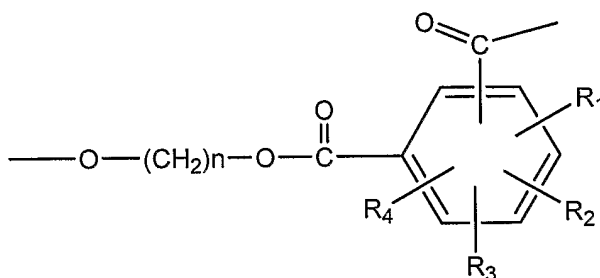
consisting of polyethylene glycol, polypropylene glycol, and polybutylene glycol. In one embodiment, the polyalkylene glycol is polyethylene glycol.

In another embodiment, the polyester is selected from the group consisting of polyethylene terephthalate, polypropylene terephthalate, and polybutylene terephthalate. In a preferred embodiment, the polyester is polybutylene terephthalate.

In one preferred embodiment, the copolymer is a polyethylene glycol/polybutylene terephthalate block copolymer (referred to herein interchangeably as PEGT/PBT or PEG/PBT copolymer).

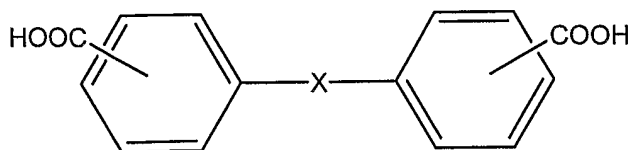
In another embodiment, the polyester has the following recurring structural formula

10 I:



I

15 wherein n is from 2 to 8, and each of R₁, R₂, R₃, and R₄ is hydrogen, halogen (such as chlorine, iodine, bromine), nitro-, or alkoxy, and each of R₁, R₂, R₃ and R₄ is the same or different. Preferably, each of R₁, R₂, R₃, and R₄ is hydrogen. Alternatively, the polyester is derived from a binuclear aromatic diacid having the following structural formula II:

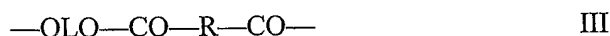


20

II

wherein X is —O—, —SO₂—, or —CH₂—.

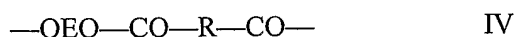
In a preferred embodiment, the copolymer is a segmented thermoplastic biodegradable polymer comprising a plurality of recurring units of the first component and
 5 units of the second component. The first component comprises about 30 weight percent to about 99 weight percent (based upon the weight of the copolymer) of units of the formula
 III:



10

wherein O represents oxygen, C represents carbon, L is a divalent organic radical remaining after removal of terminal hydroxyl groups from a poly(oxyalkylene)glycol, and R is a substituted or unsubstituted divalent radical remaining after removal of carboxyl groups from a dicarboxylic acid.

15 The second component is present in an amount of about 1 weight percent to about 70 weight percent (based upon the weight of the copolymer), and is comprised of units of the formula IV:



20

wherein E is an organic radical selected from the group consisting of a substituted or unsubstituted alkylene radical having from 2 to 8 carbon atoms, and a substituted or unsubstituted ether moiety. R is as described above in Formula III.

The poly(oxyalkylene)glycol, in one embodiment, can be selected from the group
 25 consisting of poly(oxyethylene)glycol, poly(oxypropylene)glycol, poly(oxybutylene)glycol,

and combinations thereof. Preferably, the poly(oxyalkylene)glycol is poly(oxyethylene)glycol.

The poly(oxyethylene)glycol can have a molecular weight in the range of about 200 to about 20,000, or about 200 to about 10,000. The precise molecular weight of the poly(oxyethylene)glycol is dependent upon a variety of factors, including the type of bioactive agent incorporated into the biodegradable composition.

In one embodiment, E is a radical selected from the group consisting of a substituted or unsubstituted alkylene radical having from 2 to 8 carbon atoms, preferably having from 2 to 4 carbon atoms. Preferably, the second component is selected from the group consisting of polyethylene terephthalate, polypropylene terephthalate, and polybutylene terephthalate. In one embodiment, the second component is polybutylene terephthalate.

In a preferred embodiment, the copolymer is a polyethylene glycol/polybutylene terephthalate copolymer.

In one embodiment, the polyethylene glycol/polybutylene terephthalate copolymer can be synthesized from a mixture of dimethylterephthalate, butanediol (in excess), polyethylene glycol, an antioxidant, and catalyst. The mixture is placed in a reaction vessel and heated to about 180°C, and methanol is distilled as transesterification occurs. During the transesterification, the ester bond with methyl is replaced with an ester bond with butylene and/or the polyethylene glycol. After transesterification, the temperature is raised slowly to about 245°C, and a vacuum (finally less than 0.1 mbar) is achieved. The excess butanediol is distilled and a prepolymer of butanediol terephthalate condenses with the polyethylene glycol to form a polyethylene glycol/polybutylene terephthalate copolymer. A terephthalate moiety connects the polyethylene glycol units to the polybutylene terephthalate units of the copolymer, and this copolymer is sometimes hereinafter referred to as a polyethylene glycol terephthalate/polybutylene terephthalate copolymer (also referred

to as PEGT/PBT or PEG/PBT copolymer). Alternatively, the polyethylene glycol is present as free polyethylene glycol that is mixed with PEGT/PBT copolymer. In another alternative, polyalkylene glycol/polyester copolymers can be prepared as described in U.S. Patent No. 3,908,201.

5 The above discussion of preferred copolymers is not intended to limit the invention to the specific copolymers discussed, or to any particular synthesis means thereof.

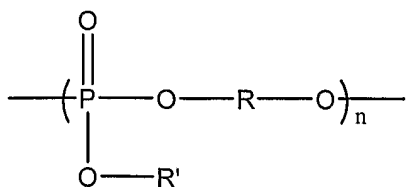
 The biodegradable composition can be formulated to provide desired degradation rates. Degradation of the biodegradable composition occurs by hydrolysis of the ester linkages, and/or oxidation of ether groups. Further, when the biodegradable composition
10 includes a bioactive agent, the formulation of the biodegradable composition can be adjusted to control the rate of diffusion of the bioactive agent from the polymer.

 In some embodiments, the degradation rate of PEGT/PBT copolymer can be controlled in two general manners. For example, the degradation rate can be increased by including hydrophilic antioxidants in the polymeric material. In addition, or alternatively,
15 the degradation rate can be increased by partially replacing the aromatic groups with aliphatic groups. For example, the more hydrophobic aromatic groups, such as terephthalate groups, can be replaced with less hydrophobic aliphatic groups, such as diacid groups (for example, succinate). In another example, more hydrophobic butylene groups can be at least partially replaced with less hydrophobic groups, such as dioxyethylene. The degree of
20 replacement can be determined to provide a selected effect on degradation rate.

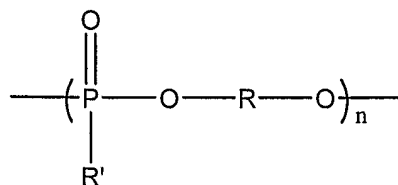
 In accordance with the invention, an increased degradation of the polyetherester copolymer is not accompanied by a significant, deleterious increase in acid formation. Degradation of the copolymer takes place by hydrolysis of ester linkages and oxidation of ether groups, which can generate a certain amount of acid. However, the levels of acid
25 generated during degradation are, in one aspect, lesser than the levels generated by other known degradable polymers (such as PLA), and in another aspect, are not deleterious to

tissues and/or bioactive agent. The acidity of the degradation environment can impact the stability of bioactive agents in that environment. Optionally, hydrophilic antioxidants can be included in the polymer material. Such hydrophilic antioxidants will be described in more detail elsewhere herein and can be particularly desirable when the biodegradable composition includes peptide or protein molecules. According to this aspect of the invention, when the protein or peptide molecule is released from the biodegradable composition upon degradation thereof, the protein is not denatured by acid degradation products. This can provide significant advantages over degradable polymers that include PLA or PLGA, where degradation increases acidity of the polymeric environment. These aspects of the invention will be described in more detail with respect to embodiments of the invention where bioactive agents are released from the biodegradable composition.

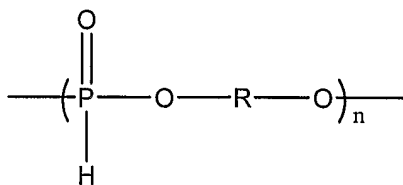
In some embodiments of the invention, the polymeric material comprises a biodegradable terephthalate copolymer that includes a phosphorus-containing linkage. Polymers having phosphoester linkages, called poly(phosphates), poly(phosphonates) and poly(phosphites), are known. See, for example, Penczek et al., Handbook of Polymer Synthesis, Chapter 17: "Phosphorus-Containing Polymers," 1077-1132 (Hans R. Kricheldorf ed., 1992), as well as U.S. Patent Nos. 6,153,212, 6,485,737, 6,322,797, 6,600,010, 6,419,709. The respective structures of each of these three classes of compounds, each having a different side chain connected to the phosphorus atom, is as follows:



Polyphosphate



Polyphosphonate



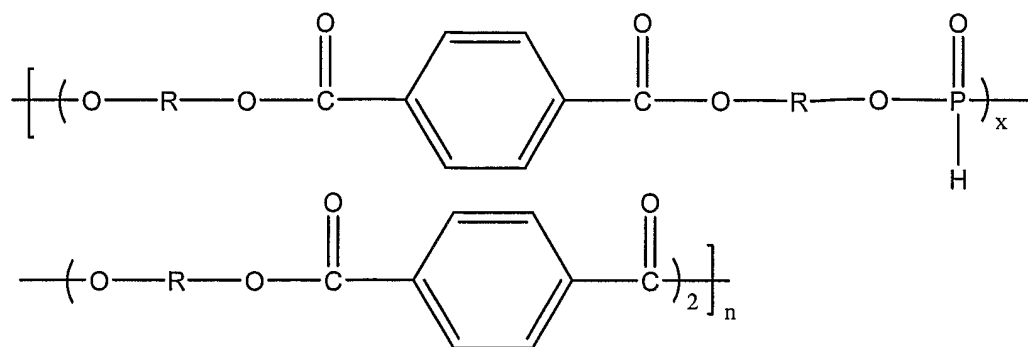
Polyphosphite

The versatility of these polymers is related to the versatility of the phosphorus atom, which is known for a multiplicity of reactions. Its bonding can involve the 3p orbitals or various 3s-3p hybrids; spd hybrids are also possible because of the accessible d orbitals. Thus, the physicochemical properties of the poly(phosphoesters) can be readily changed by varying either the R or R' group. The biodegradability of the polymeric material according to these embodiments is related to the physiologically labile phosphoester bond in the backbone of the polymer. By manipulating the backbone or the side chain, wide ranges of biodegradation rates are attainable.

An additional feature of the poly(phosphoesters) is the availability of functional side groups. Because phosphorus can be pentavalent, bioactive agents (such as drugs) can be chemically linked to the polymer. For example, bioactive agents with carboxyl groups can be coupled to the phosphorus via an ester bond, which is hydrolyzable. The P—O—C group in the backbone also lowers the glass transition temperature (T_g) of the polymer and, importantly, confers solubility in common organic solvents, which can be desirable for characterization and processing of the polymer.

In one embodiment, the terephthalate polyester includes a phosphoester linkage that is a phosphite. Suitable terephthalate polyester-polyphosphite copolymers are described, for example, in U.S. patent No. 6,419,709 (Mao et al., "Biodegradable Terephthalate Polyester-Poly(Phosphite) Compositions, Articles, and Methods of Using the Same). According to this embodiment, the polymeric material comprises recurring monomeric units of the following formula V:

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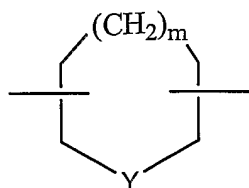
V

wherein R is a divalent organic moiety. R can be any divalent organic moiety so long as it does not interfere with the polymerization, copolymerization, or biodegradation reactions of the copolymer. Specifically, R can be an aliphatic group, for example, alkylene, such as ethylene, 1,2-dimethylethylene, n-propylene, isopropylene, 2-methylpropylene, 2,2-dimethylpropylene or tert-butylene, tert-pentylene, n-hexylene, n-heptylene, and the like; alkenylene, such as ethenylene, propenylene, dodecenylene, and the like; alkynylene, such as propynylene, hexynylene, octadecynylene, and the like; an aliphatic group substituted with a non-interfering substituent, for example, hydroxy-, halogen-, or nitrogen-substituted aliphatic group; or a cycloaliphatic group such as cyclopentylene, 2-methylcyclopentylene, cyclohexylene, and the like.

R can also be a divalent aromatic group, such as phenylene, benzylene, naphthalene, phenanthrenylene, and the like, or a divalent aromatic group substituted with a non-interfering substituent. Further, R can also be a divalent heterocyclic group, such as pyrrolylene, furanylene, thiophenylene, alkylene-pyrrolylene-alkylene, pyridylene, pyridinylene, pyrimidinylene, and the like; or can be any of these substituted with a non-interfering substituent.

Preferably, however, R is an alkylene group, a cycloaliphatic group, a phenylene group, or a divalent group having the formula VI:

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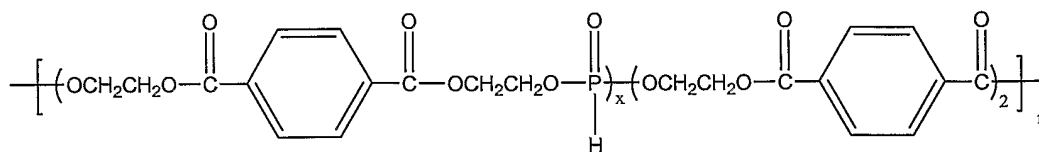
VI

wherein Y is oxygen, substituted nitrogen, or sulfur, and m is 1 to 3. In some preferred embodiments, R is an alkylene group having 1 to 7 carbon atoms and, preferably, R is an ethylene group.

5 The value of x can vary depending upon the desired solubility of the polymer, the desired T_g, the desired stability of the polymer, the desired stiffness of the final polymers, and the biodegradability and release characteristics desired in the polymer. In general, x is 1 or more, and typically, x varies between 1 and 40. In some preferred embodiments, x is in the range of 1 to 30, preferably in the range of 1 to 20, or in the range of 2 to 20.

10 The number n can vary greatly depending upon the biodegradability and the release characteristics desired in the polymer, but typically varies from about 3 to about 7,500, preferably between 5 and 5,000. In some preferred embodiments, n is in the range of about 5 to about 300, or in the range of about 5 to about 200.

15 The most common way of controlling the value of x is to vary the feed ratio of the “x” portion relative to the monomer. For example, in the case of making the polymer VII:

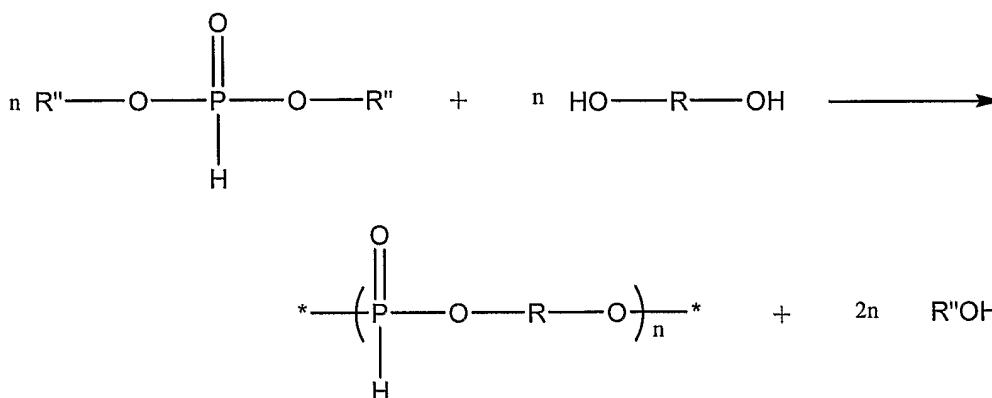


VII

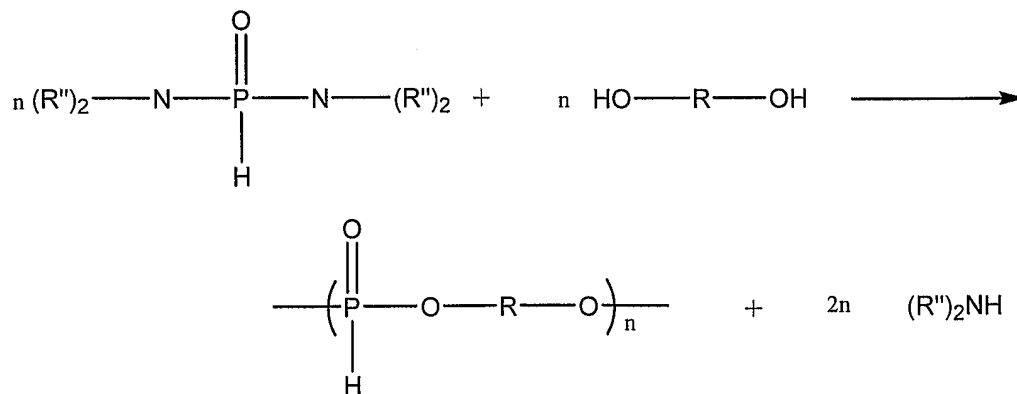
20 widely varying feed ratios of the dialkyl phosphite “x” reactant can be used with the diol reactant. Feed ratios of the reactants can easily vary from 99:1 to 1:99, for example, 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, 60:40, 55:45, 50:50, 45:55, 20:80, 15:85, and the

like. Preferably, the feed ratio between the dialkyl phosphite reactant and the diol reactant varies from about 90:10 to about 50:50, or from about 85:15 to about 50:50, or from about 80:20 to about 50:50.

The most common general reaction in preparing a poly(phosphite) is a condensation
5 of a diol with a dialkyl or diaryl phosphite according to the following equation:



Poly(phosphites) can also be obtained by employing tetraalkyldiamides of
10 phosphorus acid as condensing agents, according to the following equation:



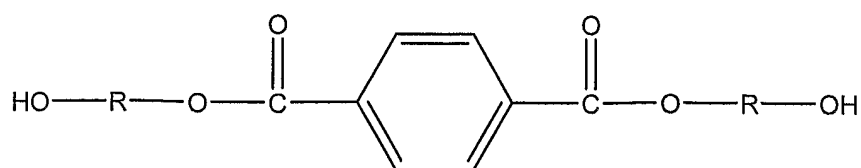
The above polymerization reactions can be either in bulk or solution
15 polymerization. An advantage of bulk polycondensation is that it avoids the use of solvents

and large amounts of other additives, thus making purification more straightforward. It can also provide polymers of reasonably high molecular weight.

Typical solvents for solution polycondensation include chlorinated organic solvents, such as chloroform, dichloromethane, or dichloroethane. The solution polymerization is preferably run in the presence of equimolar amounts of the reactants and a stoichiometric amount of an acid acceptor, usually a tertiary amine such as pyridine or triethylamine. The product is then typically isolated from the solution by precipitation with a nonsolvent and purified to remove the hydrochloride salt by conventional techniques known to those of ordinary skill in the art, such as by washing with an aqueous acidic solution, such as dilute hydrochloric acid.

Interfacial polycondensation can be used when high molecular weight polymers are desired at high reaction rates. Mild conditions minimize side reactions. Also, the dependence of high molecular weight on stoichiometric equivalence between diol and phosphite inherent in solution methods is removed. However, hydrolysis of the acid chloride may occur in the alkaline aqueous phase. Phase transfer catalysts, such as crown ethers or tertiary ammonium chloride, can be used to bring the ionized diol to the interface to facilitate the polycondensation reaction. The yield and molecular weight of the resulting polymer after interfacial polycondensation can be affected by reaction time, molar ratio of the monomers, volume ratio of the immiscible solvents, the type of acid acceptor, and the type and concentration of the phase transfer catalyst.

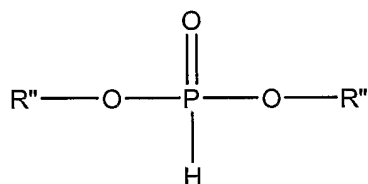
In a preferred embodiment, the process of making the biodegradable terephthalate polymer of formula V comprises the steps of polymerizing p moles of a diol compound having formula VIII:



VIII

wherein R is as defined above for formula VI, with q moles of dialkyl or diaryl of formula

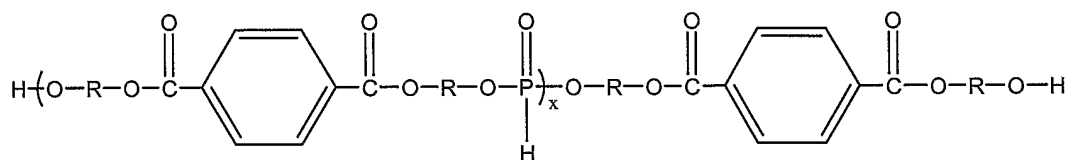
IX:



5

IX

wherein $p > q$, to form q moles of a homopolymer of formula X, shown below:

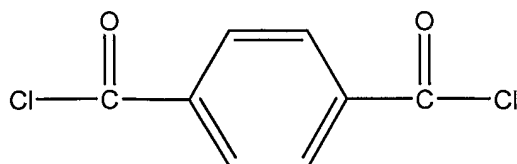


10

X

wherein R and x are as defined above for polymers V and VIII. The homopolymer so formed can be isolated, purified and used as is. Alternatively, the homopolymer, isolated or not, can be used to prepare a block copolymer composition of the invention by the steps of:

- 15 (a) polymerizing as described above, and (b) further reaction the homopolymer of formula X with (p-q) moles of terephthaloyl chloride having the formula XI:



XI

20 to form the copolymer of formula V.

The polymerization step (a) can take place at widely varying temperatures, depending upon the solvent used, the solubility desired, the molecular weight desired, and the susceptibility of the reactants to form side reactions. Preferably, however, the polymerization step (a) takes place at a temperature in the range of about -40°C to about 5 160°C ; for solution polymerization, at a temperature in the range of about 0°C to about 65°C ; for bulk polymerization, at temperatures of approximately 150°C .

The time required for the polymerization step (a) also can vary widely, depending upon the type of polymerization being used and the molecular weight desired. Preferably, however, the polymerization step (a) takes place in about 30 minutes to about 24 hours.

10 While the polymerization step (a) can be in bulk, in solution, by interfacial polycondensation, or any other convenient method of polymerization, preferably, the polymerization step (a) is a solution polymerization reaction. Particularly when solution polymerization reaction is used, an acid acceptor is advantageously present during the polymerization step (a). A particularly suitable class of acid acceptor comprises tertiary 15 amines, such as pyridine, trimethylamine, triethylamine, substituted anilines, and substituted aminopyridines. The most preferred acid acceptor is the substituted aminopyridine 4-dimethyl-aminopyridine ("DMAP").

The purpose of the copolymerization of step (b) is to form a block copolymer comprising (i) the phosphorylated homopolymer chains produced as a result of 20 polymerization step (a), and (ii) interconnecting polyester units. The result is a block copolymer having a microcrystalline structure particularly well-suited to use as a controlled release biodegradable composition.

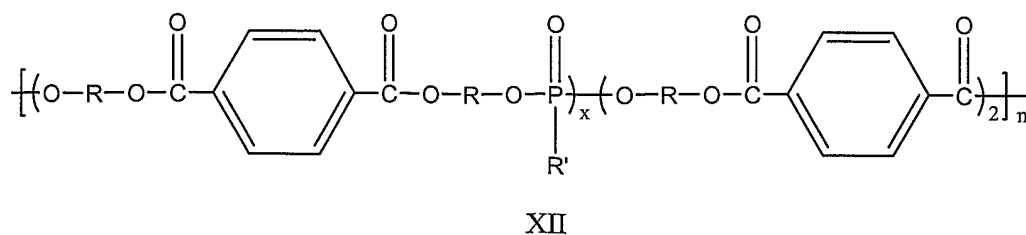
The copolymerization step (b) of the invention usually takes place at a slightly higher temperature than the temperature of the polymerization step (a), but also can vary 25 widely, depending upon the type of copolymerization reaction used, the presence of one or more catalysts, the molecular weight desired, the solubility desired, and the susceptibility of

the reactants to undesirable side reaction. However, when the copolymerization step (b) is carried out as a solution polymerization reaction, it typically takes place at a temperature in the range of about -40°C to about 100°C . Typical solvents include methylene chloride, chloroform, or any of a wide variety of inert organic solvents.

5 The time required for the copolymerization of step (b) can also vary widely, depending upon the molecular weight of the material desired and, in general, the need to use more or less rigorous conditions for the reaction to proceed to the desired degree of completion. Typically, however, the copolymerization step (b) takes place during a time of about 30 minutes to about 24 hours.

10 The terephthalate-poly(phosphite) polymer produced, whether a homopolymer or a block copolymer, is isolated from the reaction mixture by conventional techniques, such as by precipitating out, extraction with an immiscible solvent, evaporation, filtration, crystallization, and the like. Typically, however, the polymer of formula V is both isolated and purified by quenching a solution of said polymer with a non-solvent or a partial solvent,
 15 such as diethyl ether or petroleum ether.

In another embodiment, the terephthalate polyester includes a phosphoester linkage that is a phosphonate. Suitable terephthalate polyester-poly(phosphonate) copolymers are described, for example, in U.S. Patent Nos. 6,485,737 and 6,153,212 (Mao et al.,
 “Biodegradable Terephthalate Polyester-Poly(Phosphonate) Compositions, Articles and
 20 Methods of Using the Same). According to this embodiment, the polymeric material comprises recurring monomeric units shown in Formula XII:

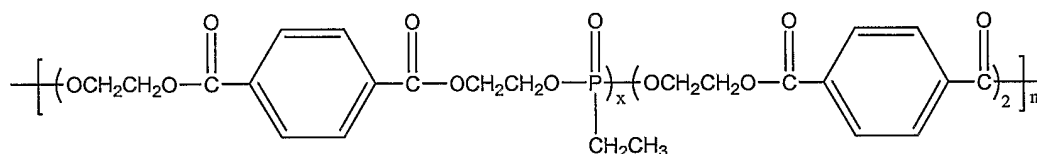


wherein R is a divalent organic moiety as defined above for terephthalate poly(phosphites) of formula V. R' in the polymeric material of this embodiment is an aliphatic, aromatic, or heterocyclic residue. When R' is aliphatic, it is preferably alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, —C₈H₁₇, and the like; or alkyl substituted with a non-interfering substituent, such as halogen, alkoxy, or nitro.

When R' is aromatic, it typically contains about 5 to about 14 carbon atoms, or about 5 to about 12 carbon atoms and, optionally, can contain one or more rings that are fused to each other. Examples of particularly suitable aromatic groups include phenyl, naphthyl, anthracenyl, phenanthryl, and the like.

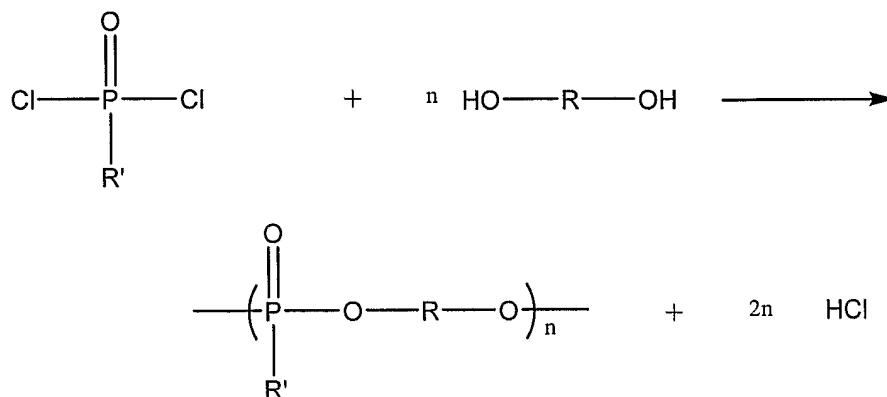
When R' is heterocyclic, it typically contains about 5 to 14 ring atoms, preferably about 5 to 12 ring atoms, and one or more heteroatoms. In one preferred embodiment, R' is an alkyl group or a phenyl group and, even more preferably, an alkyl group having 1 to 7 carbon atoms. Preferably, R' is an ethyl group.

The value of x can be varied as described above for polymeric material containing phosphite ester linkages. Similarly, one method for controlling the value of x is to vary the feed ratio of the "x" portion relative to the monomer. In this particular embodiment, feed ratios of the ethyl phosphonic dichloride "x" reactant ("EP") can be used with the terephthaloyl chloride reactant ("TC") to manufacture the polymer of formula XIII:



XIII

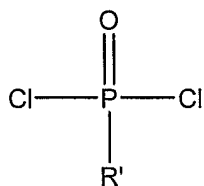
The most common general reaction in preparing a poly(phosphonate) is a dehydrochlorination between a phosphonic dichloride and a diol according to the following equation:



5

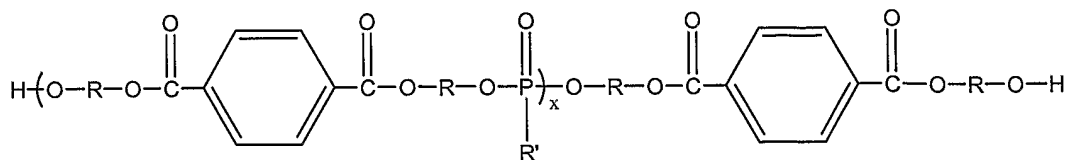
Bulk polycondensation, solution polycondensation, or interfacial polycondensation can be used to synthesize the polymers. A Friedel-Crafts reaction can also be used to synthesize poly(phosphonates). Polymerization typically is effected by reacting either
 10 bis(chloromethyl) compounds with aromatic hydrocarbons or chloromethylated diphenyl ether with triaryl phosphonates. Poly(phosphonates) can also be obtained by bulk condensation between phosphorus diimidazolides and aromatic diols, such as resorcinol and quinoline, usually under nitrogen or some other inert gas.

In one preferred embodiment, the process of making the biodegradable terephthalate
 15 polymer of formula XIII comprises the steps of polymerizing p moles of a diol compound having formula VIII above, with q moles of a phosphonic dichloride of formula XIV:



XIV

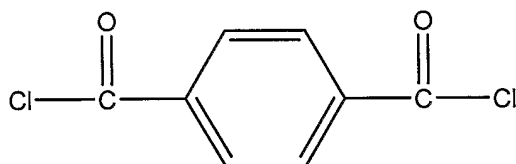
Wherein R' is defined as above, and $p > q$, to form q moles of a homopolymer of formula XV shown below:



5

XV

wherein R, R' and x are as defined above. The homopolymer so formed can be isolated, purified and used as is. Alternatively, the homopolymer, isolated or not, can be used to prepare a block copolymer composition of the invention by: (a) polymerizing as described above, and (b) further reacting the homopolymer of formula XV and excess diol of formula VIII with (p-q) moles of terephthaloyl chloride having the formula XVI:



XVI

15

to form the copolymer of formula XII.

The function of the polymerization reaction of step (a) is to phosphorylate the di-ester starting material and then to polymerize it to form the homopolymer. As described above for polymeric material containing phosphite ester linkages, the polymerization step (a) can take place at widely varying temperatures and times.

20

The addition sequence of the polymerization step (a) can vary significantly depending upon the relative reactivities of the diol of formula VIII, the phosphonic

dichloride of formula XIV, and the homopolymer of formula XV; the purity of these reactants; the temperature at which the polymerization reaction is performed; the degree of agitation used in the polymerization reaction; and the like. Preferably, however, the diol of formula VIII is combined with a solvent and an acid acceptor, and the phosphonic
5 dichloride is added slowly, for example, a solution of the phosphonic dichloride in a solvent can be trickled in or added dropwise to the chilled reaction mixture of diol, solvent, and acid acceptor, to control the rate of the polymerization reaction.

The purpose and conditions of the copolymerization of step (b) are as described above for polymeric material containing phosphite ester linkages.

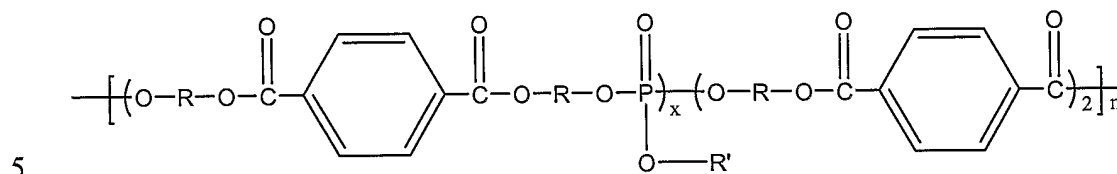
10 The polymer of formula XII, whether a homopolymer or a block polymer, is isolated from the reaction mixture by conventional techniques, such as by precipitating out, extraction with an immiscible solvent, evaporation, filtration, crystallization, and the like. Typically, however, the polymer of formula XII is both isolated and purified by quenching a solution of the polymer with a non-solvent or a partial solvent, such as diethyl ether or
15 petroleum ether.

The polymer of formula XII is usually characterized by a release rate of the bioactive agent *in vivo* that is controlled at least in part as a function of hydrolysis of the phosphoester bond or the polymer during biodegradation.

Further, the structure of the side chain can influence the release behavior of the
20 polymer. For example, it is expected that conversion of the phosphorus side chain to a more lipophilic, more hydrophobic or bulky group would slow down the degradation process. Thus, for example, release is usually faster from copolymer compositions with a small aliphatic group side chain than with a bulky aromatic side chain.

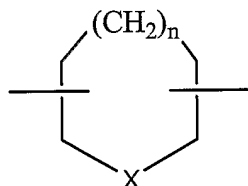
In another embodiment, the terephthalate polyester includes a phosphoester linkage
25 that is a phosphate. Suitable terephthalate polyester-poly(phosphate) copolymers are described, for example, in U.S. Patent Nos. 6,322,797 and 6,600,010 (Mao et al.,

“Biodegradable Terephthalate Polyester-Poly(Phosphate) Polymers, Compositions, Articles, and Methods for Making and Using the Same). According to this embodiment, the polymeric material comprises recurring monomeric units shown in Formula XVII:



XVII

wherein R is a divalent organic moiety as described above for terephthalate poly(phosphites) of Formula V and terephthalate poly(phosphonates) of Formula XII. Preferably, R is an alkylene group, a cycloaliphatic group, a phenylene group, or a divalent group of the formula XVIII:



XVIII

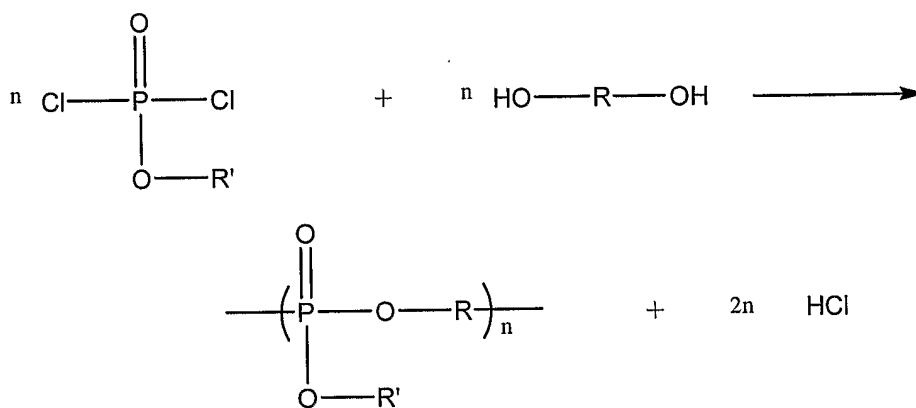
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wherein X is oxygen, substituted nitrogen, or sulfur, and n is 1 to 3. Preferably, R is an alkylene group having 1 to 7 carbon atoms and, preferably, R is an ethylene group, a 2-methyl-propylene group, or a 2,2'-dimethylpropylene group. R' is as describe above for terephthalate poly(phosphites) of Formula V and terephthalate poly(phosphonates) of Formula XII, with the proviso that R' could also comprise an alkyl conjugated to a biologically active substance to form a pendant bioactive agent delivery system. The value x is 1 or more and can vary as described for terephthalate poly(phosphites) of Formula V

20

and terephthalate poly(phosphonates) of Formula XII. Similarly, one method for controlling the value of x is to vary the feed ratio of the "x" portion relative to the other monomer (for example, varying the feed ratios of the ethyl phosphorodichloridate "x" reactant ("EOP") relative to the terephthaloyl chloride reactant ("TC")). The value n is 0 to 5,000 as described above terephthalate poly(phosphites) of Formula V and terephthalate poly(phosphonates) of Formula XII.

The most common general reaction in preparing poly(phosphates) is a dehydrochlorination between a phosphodichlorinate and a diol according to the following equation:



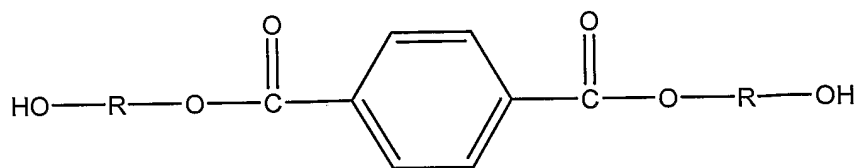
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A Friedel-Crafts reaction can also be used to synthesize poly(phosphates). The principals described above for poly(phosphonates) can be utilized for synthesis of poly(phosphates) as well. The poly(phosphates) can be synthesized via bulk polycondensation, solution polycondensation, and interfacial polycondensation as described herein.

In a preferred embodiment, the process of making a biodegradable terephthalate homopolymer of formula XVII comprises the step of polymerizing p moles of a diol compound having formula XIX:

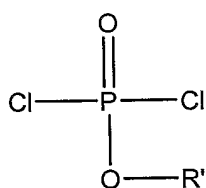
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- 40 -



XIX

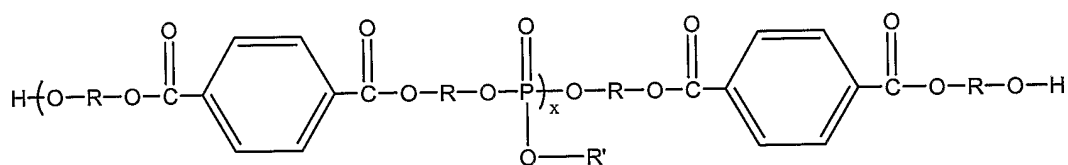
wherein R is as defined above, with q moles of a phosphorodichloridate of formula XX:



XX

5

wherein R' is defined above, and p>q, to form q moles of a homopolymer of formula XXI as shown below:



10

XXI

wherein R, R' and x are as defined above. The homopolymer so formed can be isolated, purified and used as is. Alternatively, the homopolymer, isolated or not, can be used to prepare a block copolymer by (a) polymerizing as described above, and (b) further reacting the homopolymer of formula XXI and excess diol of formula XIX with (p-q) moles of terephthaloyl chloride having the formula XVI to form the polymer of formula XVII.

The function of polymerization steps (a) and (b), as well as conditions therefor are as described above for poly(phosphonates). The addition sequence for the copolymerization

20

step (b) can vary significantly depending upon the relative reactivities of the homopolymer of formula XXI and the terephthaloyl chloride of formula XVI; the purity of these reactants; the temperature at which the copolymerization reaction is performed; the degree of agitation used in the copolymerization reaction; and the like. Preferably, however, the terephthaloyl chloride of formula XVI is added slowly to the reaction mixture, rather than vice versa. For example, a solution of the terephthaloyl chloride in a solvent can be trickled in or added dropwise to the chilled or room temperature reaction, to control the rate of the copolymerization reaction.

The polymeric materials comprising a biodegradable terephthalate copolymer that includes a phosphorus-containing linkage (poly(phosphates), poly(phosphonates) and poly(phosphites)) can comprise additional biocompatible monomeric units so long as they do not interfere with the biodegradable characteristics of the polymeric material. Such additional monomeric units can, in some embodiments, offer even greater flexibility in designing the precise release profile desired for targeted bioactive agent delivery or the precise rate of biodegradability. Examples of such additional biocompatible monomers include, but are not limited to, the recurring units found in polycarbonates, polyorthoesters, polyamides, poly(iminocarbonates), and polyanhydrides.

The polymeric material of these embodiments is preferably soluble in one or more common organic solvents for ease of fabrication and processing. Common organic solvents can include chloroform, dichloromethane, acetone, ethyl acetate, DMAC, N-methyl pyrrolidone, dimethylformamide, and dimethylsulfoxide. The polymeric material is preferably soluble in at least one of these solvents.

The T_g of the polymeric material according to these embodiments can vary widely depending upon the branching of the diols used to prepare the polymer, the relative proportion of phosphorus-containing monomer used to make the polymer, and the like.

However, preferably, the T_g is within the range of about -10°C to about 100°C, or in the range of about 0°C to about 50°C.

When working with poly(phosphates) and poly(phosphonates), the structure of the side chain can influence the release behavior of the polymer. For example, it is generally expected that, with the classes of poly(phosphoesters) described herein, conversion of the phosphorus side chain to a more lipophilic, more hydrophobic or bulky group would slow down the degradation process. For example, release would usually be faster from copolymer compositions with a small aliphatic group side chain than with a bulky aromatic side chain.

10 The terephthalate poly(phosphites) of formula V are usually characterized by a release rate of the bioactive agent *in vivo* that is controlled at least in part as a function of hydrolysis of the phosphoester bond of the polymer during biodegradation. However, poly(phosphites) do not have a side chain that can be manipulated to influence the rate of biodegradation.

15 In still further embodiments of the invention, the first polymer comprises a copolymer comprising a biodegradable, segmented molecular architecture that includes at least two different ester linkages. According to these particular embodiments, the first polymer can comprise block copolymers (of the AB or ABA type) or segmented (also known as multiblock or random-block) copolymers of the (AB)_n type. These copolymers are formed in a two (or more) stage ring opening copolymerization using two (or more) cyclic ester monomers that form linkages in the copolymer with greatly different susceptibilities to transesterification. These embodiments are described, for example, in U.S. Patent No. 5,252,701 (Jarrett et al., "Segmented Absorbable Copolymer") and will now be described in some detail herein.

25 In one aspect, the first polymer comprises a copolymer comprising a biodegradable, segmented molecular architecture that includes at least two different ester linkages.

Generally speaking, the segmented molecular architecture comprises a plurality of fast transesterifying linkages and a plurality of slow transesterifying linkages. The fast transesterifying linkages have a segment length distribution of greater than 1.3. Sequential addition copolymerization of cyclic ester monomers is utilized in conjunction with a
5 selective transesterification phenomenon to create biodegradable copolymer molecules with specific architectures.

According to the invention, the copolymer can be manufactured by sequential addition of at least two different cyclic ester monomers in at least two stages. The first cyclic ester monomer is selected from carbonates and lactones, and mixtures thereof. The
10 second cyclic ester monomer is selected from lactides and mixtures thereof. The sequential addition comprises the following steps:

- (1) first polymerizing a first stage at least the first cyclic ester monomer in the presence of a catalyst at a temperature in the range of about 160°C to about 220°C to obtain a first polymer melt;
- 15 (2) adding at least the second cyclic ester monomer to the first polymer melt; and
- (3) copolymerizing in a second stage the first polymer melt with at least the second cyclic ester monomer to obtain a second copolymer melt.

The process also comprises transesterifying the second copolymer melt for up to about 5 hours at a temperature of greater than about 180°C.

20 Another process for manufacturing a copolymer having a biodegradable, segmented molecular architecture comprises sequential addition of at least two different cyclic ester monomers in three stages. The first cyclic ester monomer is selected from carbonates, lactones, and mixtures of carbonates and lactones. The second cyclic ester monomer is selected from lactides and mixtures thereof. The sequential addition comprises the
25 following steps:

- (1) first polymerizing in a first stage at least the first cyclic ester monomer in the presence of a catalyst at a temperature in the range of about 160°C to about 220°C to obtain a first polymer melt;
- (2) first adding at least the second cyclic ester monomer to the first polymer melt;
- 5 (3) second copolymerizing in a second stage the first polymer melt with at least the second cyclic ester monomer to obtain a second copolymer melt;
- (4) second adding at least the second cyclic ester monomer to the second copolymer melt; and
- (5) copolymerizing in a third stage the second copolymer melt with at least the
10 second cyclic ester monomer to obtain a third copolymer melt.

The process also comprises transesterifying the third copolymer melt from up to about 5 hours at a temperature of greater than about 180°C.

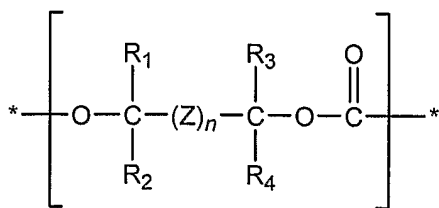
Optionally, the process can involve polymerization in the presence of a metal coordination catalyst and/or an initiator. In some embodiments, the initiator can be selected
15 from monofunctional and polyfunctional alcohols. It is generally preferred to conduct the sequential polymerization in a single reaction vessel, by sequentially adding the monomers thereto. However, if desired, one or more of the stages can be polymerized in separate reaction vessels, finally combining the stages for transesterification in a single reaction vessel. Such a process would allow the use of a cyclic polyester forming monomers for one
20 or more of the stages.

Transesterification in aliphatic polyesters derived from cyclic monomers is known in the art. For example, Gnanou and Rempp, *Macromol. Chem.*, 188:2267-2275 (1987) have described the anion polymerization of ϵ -caprolactone in the presence of lithium alkoxides as being a living polymerization that is accompanied by simultaneous reshuffling.
25 According to this reference, if reshuffling occurs between two different molecules, it can be referred to as "scrambling." If reshuffling occurs intramolecularly, it is called back-biting,

and it results in the formation of cycles, the remaining linear macromolecules are of lower molecular weight, but they still carry an active site at the chain end.

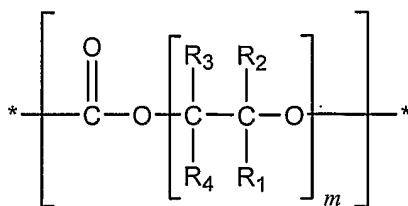
In still further embodiments, the first polymer comprises a random copolymer comprising at least one carbonate unit as the major component, the carbonate copolymerized with at least one second monomeric component. According to these embodiments, certain aliphatic carbonates can form highly crystalline random copolymers with other monomer components, so long as the appropriate carbonate is present as the major component. These copolymers can provide one or more advantages, such as relatively high modulus and tensile strength, controllable biodegradation rates, blood compatibility, and biocompatibility with living tissue. In preferred aspects, these copolymers also induce minimal inflammatory tissue reaction, as biodegradation of the carbonate polymer by hydrolytic depolymerization results in degradation substances having physiologically neutral pH. Exemplary random copolymers are described, for example, in U.S. Patent Nos. 4,891,263 (Kotliar et al.), 5,120,802 (Mares et al.), 4,916,193 (Tang et al.), 5,066,772 (Tang et al.), and 5,185,408 (Tang et al.).

According to these embodiments, the copolymers are random copolymers comprising as a minor component one or more recurring monomeric units, and as a major component, a recurring carbonate monomeric unit of the following general structures (XXII):



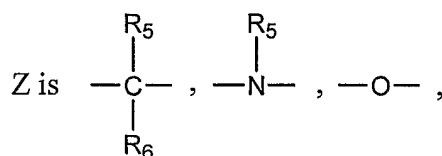
XXIIA

- 46 -



XXIIB

wherein



- 5 or combinations thereof, where Z is selected such that there are no adjacent heteroatoms; n and m are the same or different and are integers from about 1 to about 8; and R₁, R₂, R₃, and R₄ are the same or different at each occurrence and are hydrogen, alkoxyaryl, aryloxyaryl, arylalkyl, alkylarylalkyl, arylalkylaryl, alkylaryl, arylcarbonylalkyl, aryloxyalkyl, alkyl, aryl, alkylcarbonylalkyl, cycloalkyl, arylcarbonylaryl,
- 10 alkylcarbonylaryl, alkoxyalkyl, or aryl or alkyl substituted with one or more biologically compatible substituents such as alkyl, aryl, alkoxy, aryloxy, dialkylamino, diarylamino, alkylaryl amino substituents; R₅ and R₆ are the same or different and are R₁, R₂, R₃, R₄, dialkylamino, diarylamino, alkylaryl amino, alkoxy, aryloxy, alkanoyl, or arylcarbonyl; or any two of R₁ to R₆ together can form an alkylene chain completing a 3, 4, 5, 6, 7, 8, or 9
- 15 membered monocyclic, alicyclic, spiro, bicyclic, and/or tricyclic ring system, which system can optionally include one or more non-adjacent carbonyl, oxa, alkylaza, or arylaza groups; with the proviso that at least one of R₁ to R₆ is other than hydrogen.

- Illustrative of useful R₁, R₂, R₃, and R₄ groups are hydrogen; alkyl such as methyl, ethyl, propyl, butyl, pentyl, octyl, nonyl, tert-butyl, neopentyl, isopropyl, sec-butyl, dodecyl,
- 20 and the like; cycloalkyl such as cyclohexyl, cyclopentyl, cyclooctyl, cycloheptyl, and the like; alkoxyalkylene such as methoxymethylene, ethoxymethylene, butoxymethylene,

propoxyethylene, pentoxybutylene, and the like; aryloxyalkylene and aryloxyarylene such as phenoxyphenylene, phenoxyethylene and the like; and various substituted alkyl and aryl groups such as 4-dimethylaminobutyl, and the like.

Illustrative of other R₁ to R₄ groups are divalent aliphatic chains, which can optionally include one or more oxygen, trisubstituted amino or carbonyl groups, such as —

(CH₂)₂—,
 —CH₂(O)CH₂—, —(CH₂)₃—, —CH₂—CH(CH₃)—, —(CH₂)₄—, —(CH₂)₅—, —
 CH₂OCH₂—, —(CH₂)₂—N(CH₃)CH₂—, —CH₂C(O)CH₂—, —(CH₂)₂—N(CH₃)—
 (CH₂)₂—, and the like, and divalent chains to form fused, spiro, bicyclic or tricyclic ring
 10 systems, such as

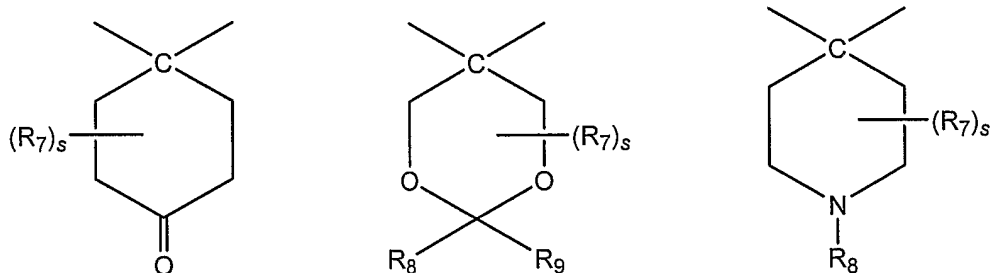
—CH(CH₂CH₂)₂CH—, —CH(CH₂CH₂CH₂)₂CH—, —CH(CH₂)(CH₂CH₂)CH—,
 —CH(CH₂)(CH₂—CH₂CH₂)CH—, —CH(C(CH₃)₂)(CH₂CH₂)CH—, and the like.

Illustrative of useful R₅ and R₆ groups are the above-listed representative R₁ to R₄ groups, including —OCH₂C(O)CH₂—, —(CH₂)₂—NCH₃—, —OCH₂C(O)CH₂—, —O—
 15 (CH₂)₂—O—, alkoxy such as propoxy, butoxy, methoxy, isopropoxy, pentoxy, nonyloxy, ethoxy, octyloxy, and the like; dialkylamino such as dimethylamino, methylethylamino, diethylamino, dibutylamino, and the like; alkanoyl such as propanoyl, acetyl, hexanoyl, and the like; arylcarbonyl such as phenylcarbonyl, p-methylphenyl carbonyl, and the like; and diarylamino and arylalkylamino such as diphenylamino, methylphenylamino,
 20 ethylphenylamino, and the like.

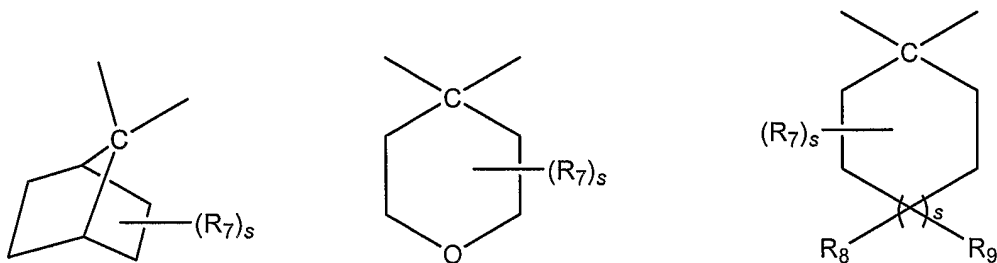
Preferred for use in accordance with these embodiment are random copolymers comprising as a major component, carbonate recurring units of structure XXIIA, wherein Z is

—(R₅—C—R₆)—, or a combination thereof; n is 1, 2, or 3; and R₁ to R₆ are as defined
 25 above, preferably where aliphatic moieties included in R₁ to R₆ include up to about 10 carbon atoms and the aryl moieties include up to about 16 carbon atoms.

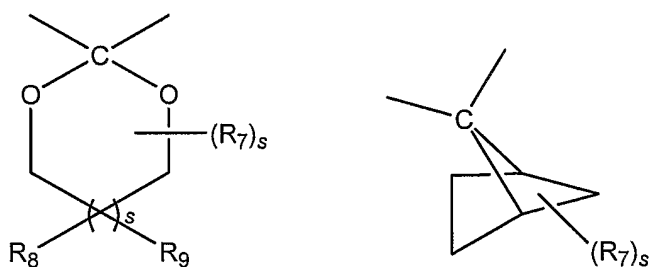
Illustrative of these preferred copolymers are those wherein, in the major component, n is 1 and Z is of the formula XXIII:



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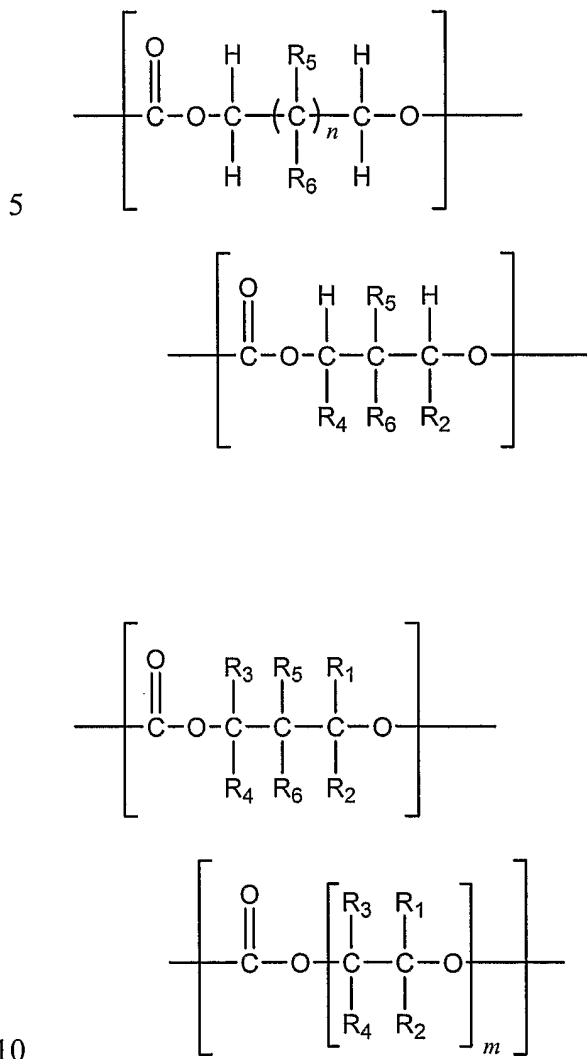


XXIII

where —C— denotes the center carbon atom of Z, when Z is —C(R₅)(R₆)—; R₇ is the same or different and is aryl, alkyl or an alkylene chain completing a 3 to 16 membered ring structure, including fused, spiro, bicyclic and/or tricyclic structures, and the like; R₈ and R₉ are the same or different at each occurrence and are R₇ or hydrogen, and s is the same or

different at each occurrence and is 0 to 3, and the open valencies are substituted with hydrogen atoms.

Also illustrative of these preferred major components are those comprising recurring units of the formula XXIV:



XXIV

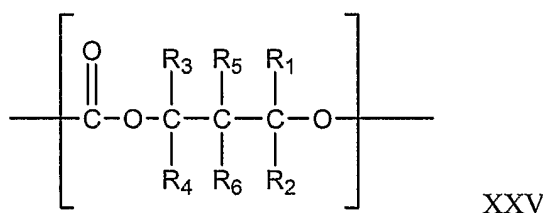
wherein:

- 15 $R_1, R_2, R_3,$ and $R_4,$ are the same or different at each occurrence and are hydrogen, alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, neopentyl, and the

like; phenyl; anisyl; phenylalkyl, such as benzyl, phenethyl, and the like; phenyl substituted with one or more alkyl or alkoxy groups such as tolyl, xylyl, p-methoxyphenyl, m-ethoxyphenyl, p-propoxyphenyl, and the like; and alkoxyalkyl such as methoxymethyl, ethoxymethyl, and the like; R₅ and R₆ are the same or different and are R₁ to R₄; alkoxy, 5 alkanoyl, arylcarbonyl, dialkylamino; or any two of R₁ to R₆ together can form alkylene chain completing 4, 5, 6, 7, 8, or 9 membered monocyclic, spiro, bicyclic and/or tricyclic ring structure which structure can optionally include one or more non-adjacent divalent carbonyl, oxa, alkylaza, or arylaza groups with the proviso that at least one of R₁ or R₆ is other than hydrogen; and

10 n and m are the same or different and are 1, 2, or 3.

Particularly preferred for use in these embodiments are random copolymers comprising as a major component, recurring units of the formula XXV:



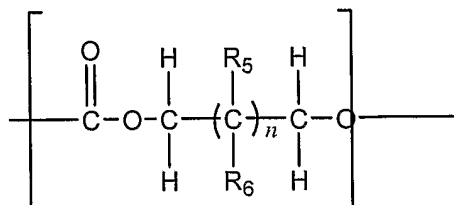
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wherein:

R₁ to R₄ are the same or different and are alkyl, hydrogen, alkoxyalkyl, phenylalkyl, alkoxyphenyl, or alkylphenyl, wherein the aliphatic moieties include 1 to 9 carbon atoms; and

20 R₅ and R₆ are the same or different at each occurrence and are selected from the group of R₁ to R₄ substituents, aryloxy, and alkoxy, or R₅ and R₆ together can form an aliphatic chain completing a 3 to 1 membered spiro, bicyclic, and/or tricyclic structure which can include one or two non-adjacent oxa, alkylaza, or arylaza groups, with the proviso that at least one of R₁ to R₄ is other than hydrogen.

Preferably, the random copolymer comprises as a major component, recurring monomeric units of the following formula XXVI:



XXVI

5 wherein:

n is 1;

R₅ and R₆ are the same or different and are hydrogen, phenyl, phenylalkyl, or phenyl or phenylalkyl substituted with one or more alkyl or alkoxy groups; or alkyl or R₅ and R₆ together make a divalent chain forming a 3 to 6 membered spiro, bicyclic, and/or tricyclic ring structure which can include one or two non-adjacent carbonyl, oxa, alkylaza, or arylaza groups, with the proviso that at least one of R₅ and R₆ is other than hydrogen.

It is preferred that the random copolymer comprises as a major component, recurring monomeric units of Formula XXVI, particularly when R₅ and R₆ are the same or different and are alkyl, phenyl, phenylalkyl, or phenyl or phenylalkyl substituted with one or more alkyl or alkoxy groups; or a divalent chain forming a 3 to 10 membered, preferably 5 to 7 membered, spiro or bicyclic ring structure that can optionally include one or two non-adjacent oxa, carbonyl, or disubstituted amino groups. It can be particularly preferred that R₅ and R₆ are the same or different and are phenyl, alkylphenyl or phenylalkyl such as tolyl, beneyl, phenethyl or phenyl, or lower alkyl of 1 to 7 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, tertiary butyl, pentyl, neopentyl, hexyl, and secondary butyl.

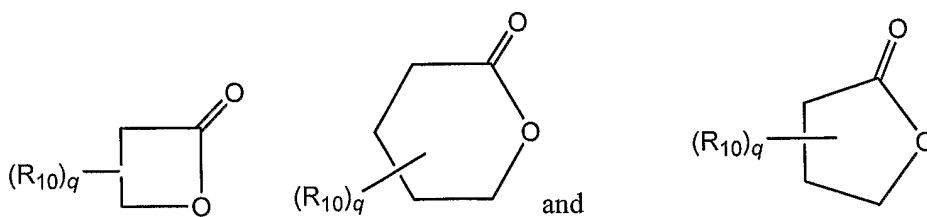
In most preferred embodiments utilizing Formula XXVI, R₅ and R₆ are the same or different, and are lower alkyl having about 1 to about 4 carbon atoms, and do not differ from each other by more than about 3 carbon atoms, and preferably by not more than about 2

- 52 -

carbon atoms. It is preferred that R_5 and R_6 be the same and comprise alkyl of about 1 to 2 carbon atoms, and preferably methyl for each of R_5 and R_6 .

According to these embodiments, the copolymers include a minor component comprising one or more other recurring monomer units. The minor component of the random copolymers of the invention can vary widely. It is preferred that the minor component is also biodegradable and bioresorbable.

Illustrative of the second recurring monomeric components are those derived from carbonates, including but not limited to certain of the monomeric units included within the scope of Formula XXIIA wherein n is 1 to 8 within $(Z)_n$, and Formula XXIIB and Formula XXVI, wherein $n=1$, particularly those less preferred as the major component, and those derived from substituted or nonsubstituted ethylene carbonates, tetramethylene carbonates, trimethylene carbonates, pentamethylene carbonates, and the like. Also illustrative of the second recurring monomeric unit are those that are derived from monomers that polymerize by ring opening polymerization as, for example, substituted and unsubstituted beta, gamma, delta, omega, and other lactones such as those of the formula XXVII:



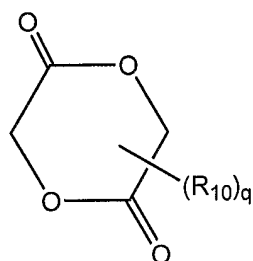
XXVII

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where R_{10} is alkoxy, alkyl or aryl, and q is 0 to 3, wherein the open valencies are substituted with hydrogen atoms. Such lactones include caprolactones, valerolactones, butyrolactones, propiolactones, and the lactones of hydroxy carboxylic acids such as 3-hydroxy-2-phenylpropanoic acid, 3-hydroxy-3-phenylpropanoic acid, 3-hydroxybutanoic acid, 3-

hydroxy-3-methylbutanoic acid, 3-hydroxypentanoic acid, 5-hydroxypentanoic acid, 3-hydroxy-4-methylheptanoic acid, 4-hydroxyocatnoic acid, and the like; and lactides such as L-lactide, D-lactide, D,L-lactide; glycolide; and dilactones such as those of the formula XXVIII:

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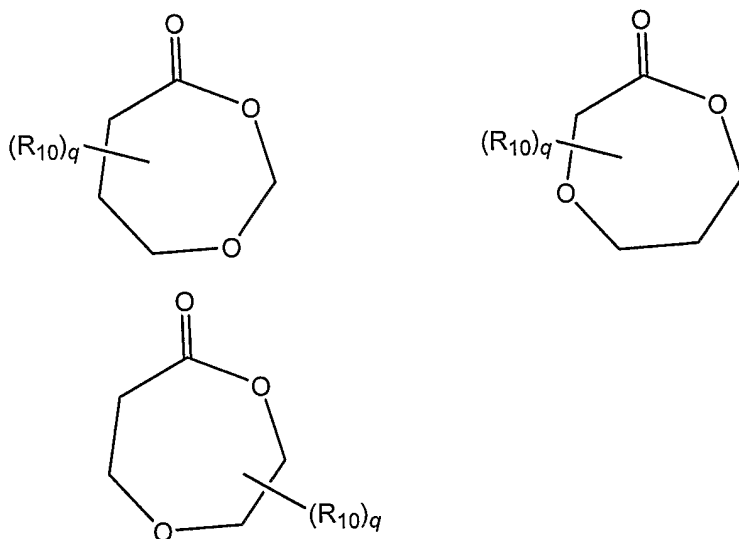


XXVIII

where R_{10} and q are as defined above in formula XXVII and where the open valencies are substituted with hydrogen atoms. Such dilactones include the dilactones of 2-
 10 hydroxybutyric acid, 2-hydroxy-2-phenylpropanoic acid, 2-hydroxyl-3-methylbutanoic acid, 2-hydroxypentanoic acid, 2-hydroxy-4-methylpentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyoctanoic acid, and the like.

Illustrative of still further useful minor components are units derived from dioxepanones such as those described in U.S. Patent No. 4,052,988 and U.K. Patent No.
 15 1,273,733. Such dioxepanones include alkyl and aryl substituted and unsubstituted dioxepanones of the formula XXIX:

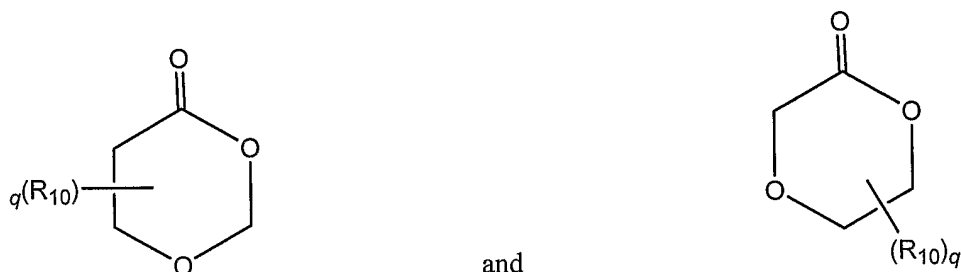
- 54 -



XXIX

5

and monomeric units derived from dioxanones such as those described in U.S. Patent Nos. 3,952,016, 4,052,988, 4,070,375, and 3,959,185, as for example, alkyl or aryl substituted and unsubstituted dioxanones of the formula XXX:



and

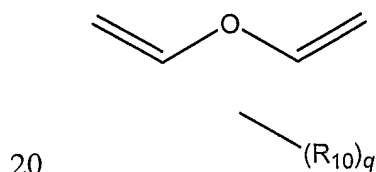
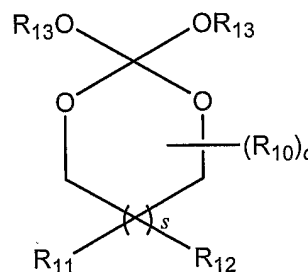
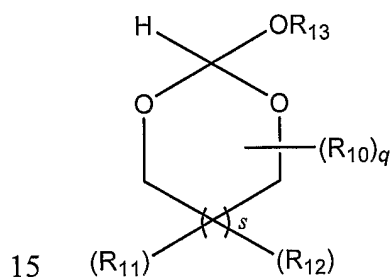
10

XXX

wherein q is as defined above; R_{10} is the same or different at each occurrence and are hydroxycarbonyl groups such as alkyl and substituted alkyl, and aryl or substituted aryl; and the open valencies are substituted with hydrogen atoms. Preferably R_{10} is the same or
 15 different and are alkyl groups containing 1 to 6 carbon atoms, preferably 1 or 2 carbon atoms, and q is 0 or 1.

Suitable minor components also include monomeric units derived from ethers such as 2,4-dimethyl-1,3-dioxane, 1,3-dioxane, 1-,4-dioxane, 2-methyl-5-methoxy-1,3-dioxane, 4-methyl-1,3-dioxane, 4-methyl-4-phenyl-1,3-dioxane, oxetane, tetrahydrofuran, tetrahydropyran, hexamethylene oxide, heptamethylene oxide, octamethylene oxide, nonamethylene oxide, and the like.

Still further minor components include monomeric units derived from epoxides such as ethylene oxide, propylene oxide, alkyl substituted ethylene oxides such as ethyl, propyl, and butyl substituted ethylene oxide, the oxides of various internal olefins such as the oxides of 2-butene, 2-pentene, 2-hexene, 3-hexene, and like epoxides; and also including units derived from epoxides with carbon dioxide; and monomeric units derived from orthoesters or orthocarbonates such as alkyl or aryl substituted or unsubstituted orthoesters, orthocarbonates, and cyclic anhydrides which may optionally include one or more oxa, alkylaza, arylaza, and carbonyl groups of the formula XXXI:



XXXI

where q and R_{10} are as described above, r is 0 to about 10, R_{13} is the same or different at each occurrence and is alkyl or aryl, and R_{11} and R_{12} are the same or different and are hydrogen, alkyl or aryl.

5 Relative percentages of each of the recurring monomeric units that make up the copolymers of these embodiments can vary widely. The only requirement is that at least one type of recurring monomeric unit within the scope of Formula XXIIA be in the major amount, and that the other type of recurring unit or units be in the minor amount. As used herein, "major amount" is more than about 50 weight% based upon the total weight of all
10 recurring monomeric units in the copolymer and "minor amount" is less than about 20 weight% based upon the total weight of all recurring monomeric units in the copolymer.

In addition, for certain applications, end-capping of these biopolymers can be desirable. End-capping can be accomplished by, for example, acylating, alkylating, silylating agents and the like.

15 Thus, the invention provides implantable devices (such as stents) that include a coating composition comprising a mixture (for example, a blend) of a first biodegradable polymer and a second biodegradable polymer. The first biodegradable polymer is preferably a polyether ester copolymer, such as PEGT/PBT. Other polymers containing ester linkages that are suitable first biodegradable polymers are described above. The
20 second polymer comprises a biodegradable polymer that is selected to provide controlled release of a bioactive agent. These aspects of the invention will now be described.

As shown in the Examples, when a coating comprising PEGT/PBT alone (i.e., an unblended PEGT/PBT coating) is formulated with a small molecule bioactive agent (such as dexamethasone), the bioactive agent is quickly released from the coating. As illustrated in
25 Example 1, for example, greater than 90% of dexamethasone is released within 24 hours from a coating composed of unblended PEGT/PBT. However, in accordance with the

invention, once a second polymer is blended with the PEGT/PBT, the initial burst of bioactive agent is controlled, allowing for more sustained release of bioactive agent for a longer period of time. Depending upon the second polymer chosen, the release of small molecular weight bioactive agents can be significantly reduced within the first 24 hours.

5 Following an initial release period, substantially linear release of bioactive agent can be achieved, thereby providing controlled release of the bioactive agent (other release profiles are also contemplated, in addition to linear release over time).

In accordance with the invention, a polyether ester copolymer (or other first polymer) is mixed with a second biodegradable polymer, to form a biodegradable coating
10 that can controllably release bioactive agent when exposed to biological conditions. The second polymer is selected to provide a controlled release of the bioactive agent. A wide variety of second polymers can be utilized in accordance with principles of the invention. Typically, the second polymer has a slower bioactive agent release rate relative to the first polymer. The second polymer can include organic esters or ethers, which when degraded
15 result in physiologically acceptable degradation products. In addition, anhydrides, amides, orthoesters, or the like, can be used. The second polymer can be composed of addition or condensation polymers, crosslinked or non-crosslinked. For the most part, besides carbon and hydrogen, the polymers will include oxygen and nitrogen, particularly oxygen. The oxygen can be present as oxy (for example, hydroxy, ether, carbonyl, and the like),
20 carboxylic acid ester, and the like. The nitrogen can be present as amide, cyano, or amino. Table 1 lists some known biodegradable polymers that can be used as the second polymer according to the invention. It is understood the invention is not limited to the polymers listed in the table; rather, this list is illustrative.

Table 1. Representative Second Biodegradable Polymers

<u>Synthetic</u>
Polypeptides
Polydepsipeptides
Polyamides
Aliphatic polyesters
Polyglycolide (PGA) and copolymers (including PEG copolymers)
Polylactide (PLA) and copolymers (including PEG copolymers)
Polyanhydrides
Poly(alkylene succinates)
Poly(hydroxy butyrate) (PHB)
Poly(caprolactone) and copolymers
Poly(butylene diglycolate)
Polydihydropyrans
Polyphosphazenes
Poly(ortho esters)
Polydioxanone (PDS)
Poly(phosphate esters)
Polyhydroxyvalerate
Poly(acetals)
Polypropylene fumarate
Trimethylene carbonates
Poly(ethyl glutamate-co-glutamic acid)
Poly(tert-butyloxy-carbonylmethyl glutamate)
Polybutyrates
Polycarbonates
Poly(ester-amides), including blends thereof

It is understood that poly(lactide) includes the naturally occurring isomer, poly(L-lactide) (PLLA), and poly(D,L-lactide) (PLA). Further, the polyanhydrides include poly[bis(p-carboxyphenoxy) propane] anhydride (PCPP) and poly(terephthalic anhydride (PTA)).

In some aspects, aliphatic polyesters can be useful second polymers. In some embodiments, aliphatic polyesters that are derived from monomers selected from lactic acid, glycolic acid, caprolactone, ethylene glycol, ethoxyphosphate, and similar monomeric units, can be useful. These polymers can be homopolymers or copolymers. Illustrative aliphatic polyesters of this nature include, but are not limited to: poly(1,4-butylene adipate-*co*-polycaprolactam); polycaprolactone; polycaprolactone diol; polyglycolide; poly(DL-lactide); poly-L-lactide; poly(DL-lactide-*co*-caprolactone) (various mole% of DL-lactide); poly(L-lactide-*co*-caprolactone-*co*-glycolide) (various MW and various mole% of DL-lactide); and poly(DL-lactide-*co*-glycolide) (various MW and various mole% of DL-lactide).

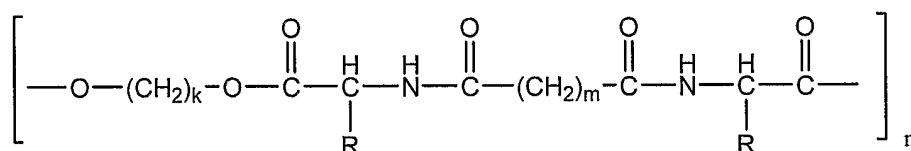
In some aspects, polyphosphoesters can be useful as second polymers, since these polymers can exhibit many properties important for bioactive agent delivery. Polyphosphoesters biodegrade through hydrolysis and possibly enzymatic digestion, and many of these polymers and copolymers are soluble in a range of organic solvents, such as THF, chloroform, acetonitrile, and ethyl acetate. In some embodiments, polyphosphoesters including monomeric units of lactide and/or ethylene glycol can be useful. Useful polyphosphoesters in accordance with the principles of the invention possess a bioactive agent elution rate that is slower than the first polymer (polyether ester copolymer), to provide controlled release of bioactive agent as contemplated herein. In some aspects, useful polyphosphoesters are soluble in a common solvent for the first polymer and bioactive agent, thereby allowing a combination of first polymer, second polymer and bioactive agent to form a true solution in the solvent.

In further aspects, the second polymer itself can comprise a mixture of polymers. For example, a blend of two or more poly(ester-amide) polymers (PEA) can be utilized, such as those described in U.S. Patent No. 6,703,040 (Katsarava et al.). Such polymers can be prepared by polymerization of a diol (D), a dicarboxylic acid (C), and an alpha-amino

acid (A) through ester and amide links in the form (DACA)_n. Illustrative amino acids include any natural or synthetic alpha-amino acid, in particular neutral amino acids.

According to these aspects, suitable diols include any aliphatic diol, such as alkylene diols like HO—(CH₂)_k—OH (i.e., non-branched), branched diols (such as propylene glycol), cyclic diols (such as dianhydrohexitols and cyclohexanediol), or oligomeric diols based on ethylene glycol (such as diethylene glycol, triethylene glycol, tetraethylene glycol, or poly(ethylene glycols)). Dicarboxylic acids can be any aliphatic dicarboxylic acid, such as α,ω-dicarboxylic acids (i.e., non-branched), branched dicarboxylic acids, cyclic dicarboxylic acids (such as cyclohexanedicarboxylic acid).

In some aspects, the PEA polymers have the following Formula XXXII:



XXXII

where k=2-12, especially 2, 3, 4 or 6; m=2-12, especially 4 or 8; and R=CH(CH₃)₂, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, (CH₂)₃CH₃, CH₂C₆H₅, or (CH₂)₃SCH₃.

In some embodiments, the second polymer comprises a mixture of a first PEA polymer in which A is L-phenylalanine (Phe-PEA) and a second PEA polymer in which A is L-leucine (Leu-PEA). The ration of Phe-PEA to Leu-PEA can be in the range of 10:1 to 1:1, or 5:1 to 2.5:1.

Optionally, the PEA polymer mixture includes an enzyme capable of hydrolytically cleaving the PEA polymer, such as α-chymotrypsin. The enzyme can be adsorbed on the surface of the biodegradable coated composition or can be included in bacteriophage that are released by action of the enzyme.

In accordance with the invention, the second polymer can be selected to compliment properties of the first polymer, such as fast bioactive agent release, relatively weak mechanical properties, and solvent solubility. In some aspects, acceptable second polymers can have slow bioactive agent release, indicating low diffusivities, which can be a function of higher glass transition temperatures, crystallinity, or specific chemical interactions with the bioactive agent.

Illustrative mechanical properties include flexibility and adhesion. For example, when the medical device to be coated with the inventive coatings is an expandable device (such as a stent), second polymers can be selected to be robust to device expansions. For example, polymers that may be considered robust can possess sufficient flexibility to accommodate device expansion, indicating that lower glass transition temperatures and lower crystallinity can be desirable. The second polymer can be selected to provide enhanced adhesion of the polymer coating to a device surface. In these aspects, unblended coatings of the first polymer can insufficiently adhere to a device surface. For example, PEGT/PBT does not typically adhere well to metal substrates. However, upon addition of a second polymer in accordance with principles of the invention, such adhesion to the device surface can be enhanced.

In some aspects, the second polymer typically dissolves in the same solvents (such as chloroform, THF, dichloromethane, and trichloromethane) as the first polymer (such as PEGT/PBT). In some embodiments, the first polymer and second polymer can be combined in a solvent to form a true solution, as described herein.

In some aspects, any number of coated layers that include blended polymer compositions as described herein can be provided to a device. The number of coated layers can be determined based upon such factors as the intended use of the device, the bioactive agent to be delivered to the patient, the number of bioactive agents to be delivered, the

desired overall thickness of the coating on the device, and the like. The blends comprising the individual coated layers can be the same or different.

In some aspects, the biodegradable composition can further include one or more coated layers that are not composed of blended polymers. Such additional coated layers can be composed of any polymer described herein, so long as the polymer is not blended with another polymer prior to application to the device. For purposes of discussion, these additional coated layers will be referred to as “unblended coated layers.” Such unblended coated layers can provide enhanced controlled release of bioactive agent. The individual polymers of such unblended coated layers can be chosen to provide a desired release rate of bioactive agent. For example, a relatively slower degrading polymer (such as PLLA) can be included as an unblended coated layer, thereby providing a slower release rate of bioactive agent from the biodegradable composition. Any unblended coated layers provided can be located at any position relative to the blended coated layers, for example, in a position more proximal to the device surface (such as adjacent the device surface or between the device surface and a blended coated layer), or distanced further from the device surface (for example, as an outermost layer or at least a layer towards the surface of the coated device that is exposed to the physiological environment during use). In some aspects, the unblended polymer of an unblended coated layer can be selected based upon characteristics of the polymer degradation products. For example, polymers that have less acidic degradation products can be chosen to provide an additional coated layer. By providing additional polymers chosen to reduce the acidity of degradation products, the acidity of the treatment site can be reduced, thereby increasing efficacy of the bioactive agent in the treatment site.

The first biodegradable polymer and second biodegradable polymer are provided as a mixture, thereby forming a bioactive agent releasing coating. In some aspects, the mixture is a blend, preferably a miscible blend, meaning that the blended composition does not

undergo significant phase separation under conditions of use (typically, the conditions of use will range from storage conditions to device usage temperatures). Typical storage temperatures can be ambient temperatures (or about 18°C to about 30°C), while typical usage temperatures can be body temperatures (or about 36°C to about 38°C). Once blended, the polymers create a coating with little bulk phase separation. Bulk phase separation can result in a coating with discrete regions of each polymer component. It is believed that such separation can allow the bioactive agent to diffuse through only one polymer, rather than a combination of both. A coating composition that experiences phase separation of the polymers can thus possess a different bioactive release rate as compared to a coating composition that does not undergo phase separation. Phase separation can occur, for example, when the polymers are chemically different or low volatility solvents are used to create the coating. Moreover, the composition of the blend can impact the miscibility of the first and second polymers. Phase separation can thus occur if too much of one of the blend components is present in the coating composition. Typically, the blended composition includes a lower amount of the first polymer (polyether ester copolymer) relative to the second polymer. For example, the first polymer can be present in an amount of about 50% or less, or about 40% or less, or about 30% or less, or about 20% or less, or about 10% or less by weight, based upon total weight of the coating composition.

Selection of the second polymer can be impacted by one or more considerations, such as, for example, the bioactive agent release rate desired for a particular application, the bioactive agent release rate of the individual polymer under consideration as a second polymer, the hydrophobicity of the individual polymer, and solvent compatibility. As an initial step, a bioactive agent is selected for treatment. Next a release rate that would provide a therapeutic dosage of the bioactive agent to a patient can be determined, based upon (for example) many of the considerations mentioned herein. Once a biodegradable composition release rate is determined, this rate can be utilized to establish parameters for

selection of the second polymer. The bioactive agent release rate for the first polymer (unblended) can be determined, as discussed herein. The bioactive agent release rate for the second polymer (unblended) can be determined, for example, utilizing information provided by the supplier of the polymer. Typically, the biodegradable composition release rate will
5 be a rate that is intermediate to the release rate of the (unblended) first polymer and (unblended) second polymer.

The relative amounts of first polymer to second polymer within the blended composition can be adjusted to further modulate the biodegradable composition release rate. In some embodiments, for example, the proportion of faster releasing polymer can be
10 increased relative to the slower releasing polymer to provide a faster biodegradable composition release rate. In some embodiments, when most of the bioactive agent dosage is desired to be released over a long time period, the proportion of slower releasing polymer can be increased relative to the faster releasing polymer within the blended composition.

The relative hydrophobicity of the second polymer can impact release rate of the
15 bioactive agent. For example, blended compositions composed of PEGT/PBT (which is a relatively hydrophilic copolymer), a more hydrophobic second polymer can be chosen to modulate the release profile of bioactive agent over time.

Another selection parameter for the second polymer is solvent compatibility. In some preferred aspects, the solvent system for the first polymer and second polymer are
20 compatible. In further aspects, the solvent system for the first polymer, second polymer, and bioactive agent are compatible. In some aspects, as described above, the first polymer and second polymer can be combined in a solvent to form a true solution. In further aspects, the first biodegradable polymer second biodegradable polymer and bioactive agent are combined to form a true solution. Further, the first polymer and second polymer can be
25 formulated to provide a coating solution that is easily applied to a device surface. For example, when it is desirable to apply the coating solution to a device surface utilizing spray

techniques, it can be useful to form a coating solution that provides good atomization for such application, without undergoing phase separation during the application process.

The principle mode of degradation for many of the biodegradable polymers (and particularly the lactide and glycolide polymers and copolymers) is hydrolysis. Degradation proceeds first by diffusion of water into the material followed by random hydrolysis, fragmentation of the material, and finally a more extensive hydrolysis accompanied by phagocytosis, diffusion, and metabolism. The hydrolysis can be affected by the size and hydrophilicity of the particular polymer material, the crystallinity of the polymer, and the pH and temperature of the environment.

Once the polymer is hydrolyzed, the products of hydrolysis are either metabolized or secreted. The lactic acid generated by the hydrolytic degradation of PLA becomes incorporated into the tricarboxylic acid cycle and is secreted as carbon dioxide and water. Polyglycolic acid (PGA) is also broken down by random hydrolysis accompanied by non-specific enzymatic hydrolysis to glycolic acid that is either secreted or enzymatically converted to other metabolized species.

In some aspects, degradation of PLA, PGA and the like can generate an acidic environment in proximity to the device. Such acidic conditions can adversely impact bioactive agent, biodegradable polymer, or both. In preferred aspects, the inventive biodegradable compositions are formulated such that the amount of acidic degradation products (such as those generated upon degradation of PLLA or PLGA) are controlled to reduce or minimize risk of damage to bioactive agent provided in the biodegradable compositions. Since many bioactive agents are acid-sensitive, it can be beneficial to provide biodegradable compositions that can reduce the amount of biodegradable polymer that could create an acidic environment upon degradation, and/or provide a protective environment for such bioactive agents.

In some aspects, the biodegradable composition comprises a blend of a first polymer comprising PEGT/PBT copolymer, and a second polymer composed of PLLA. These embodiments deliver bioactive agent over a longer time period, and with a lower initial release rate, relative to embodiments having a biodegradable composition composed of a single polymer (for example, a single polymer of either PEGT/PBT copolymer or PLLA). The relative amounts of the first polymer and second polymer can be adjusted to achieve the desired combination of initial dosage rate and subsequent constant and longer lasting dosage rate.

The blended coatings include a first polymer and a second polymer, where the second polymer typically has a slower bioactive release rate than the first polymer. While not intending to be bound by a particular theory, it is believed that selection of the second polymer and the amount of second polymer provided in the biodegradable composition can impact biocompatibility and degradation rate of the biodegradable composition.

In some aspects, the identity and/or relative amount of the first polymer within the biodegradable composition can improve coating biocompatibility. In one such preferred embodiment, presence of PEGT/PBT copolymer in sufficient amounts can improve coating biocompatibility by presenting a surface that generates significantly less acid relative to PLLA, PDLLA, PLGA, or the like during degradation than the hydrophobic biodegradable polymers. As a result, at least the implantation site (and perhaps a larger area surrounding the implanted device) will be less acidic during degradation of the biodegradable composition.

In some aspects, the biodegradable composition includes PEGT/PBT copolymer in an amount in the range of about 2% to about 50% by weight, or in the range of about 5% to about 35% by weight, based upon the total weight of the biodegradable composition. In some aspects, the biodegradable composition includes PLLA in an amount in the range of about 50% to about 98% by weight, or in the range of about 65% to about 95% by weight,

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based upon the total weight of the biodegradable composition. The relative amounts of PEGT/PBT copolymer and more hydrophobic polymer (such as PLLA, PLGA, PGA, or the like) can be adjusted to achieve the desired combination of high initial dosage rate and subsequent lower but longer lasting dosage rate. As shown in the examples, the relative amounts of the first polymer and second polymer can be adjusted to achieve the desired release profile.

Suitable solvents that can be used to formulate the biodegradable composition include, but are not limited to, chloroform, water, alcohol (including, for example, methyl, ethyl, isopropyl and the like), acetone, acetonitrile, ether, methyl ethyl ketone (MEK), ethyl acetate, tetrahydrofuran (THF), dioxane, methylene chloride, xylene, toluene, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMAC), N-methylpyrrolidone (NMP), dichloromethane, hexane, combinations of these, and the like.

To form biodegradable composition with bioactive agent, the selected biodegradable polymers are blended and mixed with a bioactive agent. The solvent systems for the first and second polymers are preferably compatible. The bioactive agent can be present as a liquid, a finely divided solid, or any other appropriate physical form. The variety of different bioactive agents that can be used in conjunction with the polymers of the invention is vast. The inventive biodegradable compositions can find particular utility for delivery of small molecular weight bioactive agents, as described herein. Optionally, the biodegradable composition can include one or more additives, such as diluents, carriers, excipients, stabilizers, or the like.

Upon contact with body fluids, the biodegradable composition undergoes gradual degradation (mainly through hydrolysis) with concomitant release of the bioactive agent for a sustained or extended period. This can result in prolonged delivery (such as a period of several weeks) of therapeutically effective amounts of the bioactive agent. The

therapeutically effective amount can be determined based upon such factors as the patient being treated, the severity of the condition, the judgment of the prescribing physician, and the like. In light of the teaching herein, those skilled in the art will be capable of preparing a variety of formulations.

5 The various Examples and corresponding figures illustrate the changes in elution rates possible with variation in biodegradable composition. As illustrated in the Examples and the discussion herein, the inventive devices and methods can provide the ability to control the rate of release of bioactive agent by altering the formulation of the coating composition (for example, by providing the first polymer and second polymer in different
10 relative amounts, and/or by altering the amount of bioactive agent included in the coating composition). As illustrated in the Examples, differences in release rates were observed among the coated compositions, which relate to differences in polymer composition of the coated compositions. Thus, in some aspects, the polymer composition of the coating compositions can be manipulated to control the release rate of the bioactive agent.

15 In accordance with principles of the invention, each coating system has its own release kinetics profile that can be adjusted by polymeric composition. The biodegradable compositions of the invention include one or more bioactive agents, thereby providing a drug-delivery device. These drug-delivery aspects will now be described in more detail.

 As used herein, "bioactive agent" refers to an agent that affects physiology of
20 biological tissue. Bioactive agents useful according to the invention include virtually any substance that possesses desirable therapeutic characteristics for application to the implantation site.

 For ease of discussion, reference will repeatedly be made to a "bioactive agent." While reference will be made to a "bioactive agent," it will be understood that the invention
25 can provide any number of bioactive agents to a treatment site. Thus, reference to the singular form of "bioactive agent" is intended to encompass the plural form as well.

Moreover, for purposes of discussion, reference will be made to association of the bioactive agent with a biodegradable composition composed of blends of PEGT/PBT and a second polymer, such as PLA. However, it will be apparent upon review of this disclosure that the bioactive agent can be associated with any of the biodegradable polymeric compositions described herein. Further, the additives described herein are applicable to all polymer systems disclosed as well.

Exemplary bioactive agents include, but are not limited to, thrombin inhibitors, antithrombogenic agents, thrombolytic agents, fibrinolytic agents, anticoagulants, anti-platelet agents, vasospasm inhibitors, calcium channel blockers, steroids, vasodilators, anti-hypertensive agents, antimicrobial agents, antibiotics, antibacterial agents, antiparasite and/or antiprotozoal solutes, antiseptics, antifungals, angiogenic agents, anti-angiogenic agents, inhibitors of surface glycoprotein receptors, antimetabolites, microtubule inhibitors, antiseptory agents, actin inhibitors, remodeling inhibitors, antisense nucleotides, anti-metabolites, mitotic agents, anti-proliferatives, anticancer chemotherapeutic agents, anti-neoplastic agents, antipolymerases, antivirals, anti-AIDS substances, anti-inflammatory steroids or non-steroidal anti-inflammatory agents, analgesics, antipyretics, immunosuppressive agents, immunomodulators, growth hormone antagonists, growth factors, radiotherapeutic agents, peptides, proteins, enzymes, extracellular matrix components, ACE inhibitors, free radical scavengers, chelators, anti-oxidants, photodynamic therapy agents, gene therapy agents, anesthetics, immunotoxins, neurotoxins, opioids, dopamine agonists, hypnotics, antihistamines, tranquilizers, anticonvulsants, muscle relaxants and anti-Parkinson substances, antispasmodics and muscle contractants, anticholinergics, ophthalmic agents, antiglaucoma solutes, prostaglandins, antidepressants, antipsychotic substances, neurotransmitters, anti-emetics, imaging agents, specific targeting agents, and cell response modifiers.

More specifically, in embodiments the active agent can include heparin, covalent heparin, synthetic heparin salts, or another thrombin inhibitor; hirudin, hirulog, argatroban, D-phenylalanyl-L-poly-L-arginyl chloromethyl ketone, or another antithrombogenic agent; urokinase, streptokinase, a tissue plasminogen activator, or another thrombolytic agent; a
5 fibrinolytic agent; a vasospasm inhibitor; a calcium channel blocker, a nitrate, nitric oxide, a nitric oxide promoter, nitric oxide donors, dipyridamole, or another vasodilator; HYTRIN® or other antihypertensive agents; a glycoprotein IIb/IIIa inhibitor (abciximab) or another inhibitor of surface glycoprotein receptors; aspirin, ticlopidine, clopidogrel or another antiplatelet agent; colchicine or another antimitotic, or another microtubule inhibitor;
10 dimethyl sulfoxide (DMSO), a retinoid, or another antisecretory agent; cytochalasin or another actin inhibitor; cell cycle inhibitors; remodeling inhibitors; deoxyribonucleic acid, an antisense nucleotide, or another agent for molecular genetic intervention; methotrexate, or another antimetabolite or antiproliferative agent; tamoxifen citrate, TAXOL®, paclitaxel, or the derivatives thereof, rapamycin (or other rapalogs, e.g. ABT-578 or sirolimus),
15 vinblastine, vincristine, vinorelbine, etoposide, tenoposide, dactinomycin (actinomycin D), daunorubicin, doxorubicin, idarubicin, anthracyclines, mitoxantrone, bleomycin, plicamycin (mithramycin), mitomycin, mechlorethamine, cyclophosphamide and its analogs, chlorambucil, ethylenimines, methylmelamines, alkyl sulfonates (e.g., busulfan), nitrosoureas (carmustine, etc.), streptozocin, methotrexate (used with many indications),
20 fluorouracil, floxuridine, cytarabine, mercaptopurine, thioguanine, pentostatin, 2-chlorodeoxyadenosine, cisplatin, carboplatin, procarbazine, hydroxyurea, morpholino phosphorodiamidate oligomer or other anti-cancer chemotherapeutic agents; cyclosporin, tacrolimus (FK-506), pimecrolimus, azathioprine, mycophenolate mofetil, mTOR inhibitors, or another immunosuppressive agent; cortisol, cortisone, dexamethasone, dexamethasone
25 sodium phosphate, dexamethasone acetate, dexamethasone derivatives, betamethasone, fludrocortisone, prednisone, prednisolone, 6U-methylprednisolone, triamcinolone (e.g.,

triamcinolone acetonide), or another steroidal agent; trapidil (a PDGF antagonist),
angiopiptin (a growth hormone antagonist), angiogenin, a growth factor (such as vascular
endothelial growth factor (VEGF)), or an anti-growth factor antibody (e.g., ranibizumab,
which is sold under the tradename LUCENTIS[®]), or another growth factor antagonist or
5 agonist; dopamine, bromocriptine mesylate, pergolide mesylate, or another dopamine
agonist; ⁶⁰Co (5.3 year half life), ¹⁹²Ir (73.8 days), ³²P (14.3 days), ¹¹¹In (68 hours), ⁹⁰Y (64
hours), ⁹⁹Tc (6 hours), or another radiotherapeutic agent; iodine-containing compounds,
barium-containing compounds, gold, tantalum, platinum, tungsten or another heavy metal
functioning as a radiopaque agent; a peptide, a protein, an extracellular matrix component, a
10 cellular component or another biologic agent; captopril, enalapril or another angiotensin
converting enzyme (ACE) inhibitor; angiotensin receptor blockers; enzyme inhibitors
(including growth factor signal transduction kinase inhibitors); ascorbic acid, alpha
tocopherol, superoxide dismutase, deferoxamine, a 21-aminosteroid (lasaroid) or another
free radical scavenger, iron chelator or antioxidant; a ¹⁴C-, ³H-, ¹³¹I-, ³²P- or ³⁶S-
15 radiolabelled form or other radiolabelled form of any of the foregoing; an estrogen (such as
estradiol, estriol, estrone, and the like) or another sex hormone; AZT or other
antipolymerases; acyclovir, famciclovir, rimantadine hydrochloride, ganciclovir sodium,
Norvir, Crixivan, or other antiviral agents; 5-aminolevulinic acid, meta-
tetrahydroxyphenylchlorin, hexadecafluorozinc phthalocyanine, tetramethyl
20 hematoporphyrin, rhodamine 123 or other photodynamic therapy agents; an IgG2 Kappa
antibody against *Pseudomonas aeruginosa* exotoxin A and reactive with A431 epidermoid
carcinoma cells, monoclonal antibody against the noradrenergic enzyme dopamine beta-
hydroxylase conjugated to saporin, or other antibody targeted therapy agents; gene therapy
agents; enalapril and other prodrugs; PROSCAR[®], HYTRIN[®] or other agents for treating
25 benign prostatic hyperplasia (BHP); mitotane, aminoglutethimide, breveldin,
acetaminophen, etodalac, tolmetin, ketorolac, ibuprofen and derivatives, mefenamic acid,

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meclofenamic acid, piroxicam, tenoxicam, phenylbutazone, oxyphenbutazone, nabumetone, auranofin, aurothioglucose, gold sodium thiomalate, a mixture of any of these, or derivatives of any of these.

Other biologically useful compounds that can also be included in the coating material include, but are not limited to, hormones, β -blockers, anti-anginal agents, cardiac inotropic agents, corticosteroids, analgesics, anti-inflammatory agents, anti-arrhythmic agents, immunosuppressants, anti-bacterial agents, anti-hypertensive agents, anti-malarials, anti-neoplastic agents, anti-protozoal agents, anti-thyroid agents, sedatives, hypnotics and neuroleptics, diuretics, anti-parkinsonian agents, gastro-intestinal agents, anti-viral agents, anti-diabetics, anti-epileptics, anti-fungal agents, histamine H-receptor antagonists, lipid regulating agents, muscle relaxants, nutritional agents such as vitamins and minerals, stimulants, nucleic acids, polypeptides, and vaccines.

Antibiotics are substances that inhibit the growth of or kill microorganisms. Antibiotics can be produced synthetically or by microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vancomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromycin, geldanamycin, geldanamycin analogs, cephalosporins, or the like. Examples of cephalosporins include cephalothin, cephapirin, cefazolin, cephalexin, cephradine, cefadroxil, cefamandole, cefoxitin, cefaclor, cefuroxime, cefonicid, ceforanide, cefotaxime, moxalactam, ceftizoxime, ceftriaxone, and cefoperazone.

Antiseptics are recognized as substances that prevent or arrest the growth or action of microorganisms, generally in a nonspecific fashion, e.g., either by inhibiting their activity or destroying them. Examples of antiseptics include silver sulfadiazine, chlorhexidine, glutaraldehyde, peracetic acid, sodium hypochlorite, phenols, phenolic compounds, iodophor compounds, quaternary ammonium compounds, and chlorine compounds.

Antiviral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include α -methyl-1-adamantanemethylamine, hydroxy-ethoxymethylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

5 Enzyme inhibitors are substances that inhibit an enzymatic reaction. Examples of enzyme inhibitors include edrophonium chloride, N-methylphysostigmine, neostigmine bromide, physostigmine sulfate, tacrine HCL, tacrine, 1-hydroxy maleate, iodotubercidin, p-bromotetramisole, 10-(α -diethylaminopropionyl)-phenothiazine hydrochloride, calmidazolium chloride, hemicholinium-3,3,5-dinitrocatechol, diacylglycerol kinase
10 inhibitor I, diacylglycerol kinase inhibitor II, 3-phenylpropargylamine, N-monomethyl-L-arginine acetate, carbidopa, 3-hydroxybenzylhydrazine HCl, hydralazine HCl, clorgyline HCl, deprenyl HCl L(-), deprenyl HCl D(+), hydroxylamine HCl, iproniazid phosphate, 6-MeO-tetrahydro-9H-pyrido-indole, nialamide, pargyline HCl, quinacrine HCl, semicarbazide HCl, tranylcypromine HCl, N,N-diethylaminoethyl-2,2-di-phenylvalerate
15 hydrochloride, 3-isobutyl-1-methylxanthine, papaverine HCl, indomethacin, 2-cyclooctyl-2-hydroxyethylamine hydrochloride, 2,3-dichloro- α -methylbenzylamine (DCMB), 8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride, p-aminoglutethimide, p-aminoglutethimide tartrate R(+), p-aminoglutethimide tartrate S(-), 3-iodotyrosine, alpha-methyltyrosine L(-), alpha-methyltyrosine D(-), cetazolamide, dichlorphenamide, 6-
20 hydroxy-2-benzothiazolesulfonamide, and allopurinol.

Anti-pyretics are substances capable of relieving or reducing fever. Anti-inflammatory agents are substances capable of counteracting or suppressing inflammation. Examples of such agents include aspirin (salicylic acid), indomethacin, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac,
25 diflunisal, diclofenac, indoprofen and sodium salicylamide.

Local anesthetics are substances that have an anesthetic effect in a localized region. Examples of such anesthetics include procaine, lidocaine, tetracaine and dibucaine.

Imaging agents are agents capable of imaging a desired site, e.g., tumor, *in vivo*. Examples of imaging agents include substances having a label that is detectable *in vivo*,
5 e.g., antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (PDGF). Other chemotactic factors include neutrophil-activating protein, monocyte chemoattractant protein, macrophage-inflammatory protein, SIS (small inducible secreted),
10 platelet factor, platelet basic protein, melanoma growth stimulating activity, epidermal growth factor, transforming growth factor alpha, fibroblast growth factor, platelet-derived endothelial cell growth factor, insulin-like growth factor, nerve growth factor, bone growth/cartilage-inducing factor (alpha and beta), and matrix metalloproteinase inhibitors. Other cell response modifiers are the interleukins, interleukin receptors, interleukin
15 inhibitors, interferons, including alpha, beta, and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, activin, and DNA that encodes for the production of any of these proteins, antisense
20 molecules, androgenic receptor blockers and statin agents.

In an embodiment, the active agent can be in a microparticle. In an embodiment, microparticles can be dispersed on the surface of the substrate.

The weight of the coating attributable to the active agent can be in any range desired for a given active agent in a given application. In some embodiments, weight of the coating
25 attributable to the active agent is in the range of about 1 microgram to about 10 milligrams of active agent per cm² of the effective surface area of the device. By "effective" surface

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area it is meant the surface amenable to being coated with the composition itself. For a flat, nonporous, surface, for instance, this will generally be the macroscopic surface area itself, while for considerably more porous or convoluted (e.g., corrugated, pleated, or fibrous) surfaces the effective surface area can be significantly greater than the corresponding macroscopic surface area. In an embodiment, the weight of the coating attributable to the active agent is between about 0.01 mg and about 0.5 mg of active agent per cm² of the gross surface area of the device. In an embodiment, the weight of the coating attributable to the active agent is greater than about 0.01 mg.

In some embodiments, more than one active agent can be used in the coating. Specifically, co-agents or co-drugs can be used. A co-agent or co-drug can act differently than the first agent or drug. The co-agent or co-drug can have an elution profile that is different than the first agent or drug.

In some embodiments, the active agent can be hydrophilic. In an embodiment, the active agent can have a molecular weight of less than 1500 daltons and can have a water solubility of greater than 10mg/ml at 25 °C. In some embodiments, the active agent can be hydrophobic. In an embodiment, the active agent can have a water solubility of less than 10mg/ml at 25 °C.

Biodegradable compositions can be formulated by mixing one or more bioactive agents with the polymers. The bioactive agent can be present as a liquid, a finely divided solid, or any other appropriate physical form. Typically, but optionally, the biodegradable composition will include one or more additives, such as diluents, carriers, excipients, stabilizers, or the like.

The particular bioactive agent, or combination of bioactive agents, can be selected depending upon one or more of the following factors: the application of the device (for example, coronary stent, orthopedic device, fixation element), the amount of the device composed of the polymeric material (for example, fabricating the entire device of polymeric

material, versus providing the polymeric material as a coating on a device substrate), the medical condition to be treated, the anticipated duration of treatment, characteristics of the implantation site, the number and type of bioactive agents to be utilized, and the like.

The concentration of the bioactive agent in the biodegradable composition can be in
5 the range of about 0.01% to about 75% by weight, or about 0.01% to about 50%, or about
1% to about 35%, or about 1% to about 20%, or about 1% to about 10% by weight, based on
the weight of the final biodegradable composition. In some aspects, the bioactive agent is
present in the biodegradable composition in an amount in the range of about 75% by weight
or less, or about 50% by weight or less, or about 35% or less, or about 25% or less, or about
10 10% or less. The amount of bioactive agent in the biodegradable composition can be in the
range of about 1 μg to about 10 mg, or about 100 μg to about 1000 μg , or about 300 μg to
about 600 μg .

In some aspects, the bioactive agent should be stable in the selected solvent for the
coating composition. For example, some organic solvents can adversely impact bioactive
15 agent stability, particularly when the bioactive agent is present in the solvent over time. In
some embodiments, bioactive agents such as rapamycin can be adversely impacted (e.g.,
degrade) over time when present in an aqueous solution. Thus, selection of solvent system
for the coating compositions can be determined in part by consideration of the bioactive
agent to be delivered from a medical article.

20 In one illustrative embodiment, when a relatively small-sized bioactive agent (for
example, many antimicrobial agents, antiviral agents, and the like) is included in a
PEGT/PBT polymeric material, the polyethylene glycol component of the copolymer
preferably has a molecular weight in the range of about 200 to about 10,000, or about 300 to
about 4,000. Also, the polyethylene glycol terephthalate is preferably present in the
25 copolymer in an amount in the range of about 30 weight percent to about 80 weight percent
of the weight of the copolymer, or in the range of about 50 weight percent to about 60

weight percent of the weight of the copolymer. According to these particular embodiments, the polybutylene terephthalate is present in the copolymer in an amount in the range of about 20 weight percent to about 70 weight percent of the copolymer, or in the range of about 40 weight percent to about 50 weight percent of the copolymer.

5 In some aspects, it can be desirable to provide one or more additives to the one or more of the polymers of the biodegradable composition. Such additives can be particularly desirable when bioactive agent is included in the polymer comprising the biodegradable composition. Additives can be included to impact the release of bioactive agent from the device. Suitable additives according to these aspects include, but are not limited to,
10 hydrophobic antioxidants, hydrophobic molecules, and hydrophilic antioxidants, and excipients. Alternatively, additives can be included to impact imaging of the device once implanted. Illustrative additives will now be described in more detail. However, it is understood that such additives are optional; in some aspects, the inventive coating compositions do not require any additive to impact release of bioactive agent, since
15 selection of first polymer and second polymer, as well as relative amounts of each polymer, can achieve a wide variety of bioactive agent release rates without use of additives. Thus, in some embodiments, any additives utilized are useful for other features of the coating, besides the bioactive agent release rate.

 In some embodiments, one or more of the polymers comprising the biodegradable
20 composition can optionally include at least one hydrophobic antioxidant. For example, when the polyetherester material (such as PEGT/PBT) includes a hydrophobic small-sized drug (such as, for example, a steroid hormone), the polymer material can include at least one hydrophobic antioxidant. Exemplary hydrophobic antioxidants that can be employed include, but are not limited to, butylated hydroxytoluene (BHT) tocopherols (such as α -
25 tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, ϵ -tocopherol, ζ_1 -tocopherol, ζ_2 -tocopherol, and η -tocopherol), and ascorbic acid 6-palmitate. Such hydrophobic

antioxidants can retard the degradation of the polyetherester copolymer material, and can retard the release of the bioactive agent contained in the polymer. Thus, the use of a hydrophobic or lipophilic antioxidant can be desirable particularly to the formation of biodegradable compositions that include drugs that tend to be released quickly from the polymer, such as, for example, small drug molecules having a molecular weight less than 1500 (in other words, the use of a hydrophobic or lipophilic antioxidant can slow release of the drug from the biodegradable composition if desired). In some embodiments, the antioxidant can improve drug stability as well. For example, inclusion of rapamycin in drug eluting stents ("DES") can be problematic, as rapamycin can be less stable than desired. Thus, inclusion of a hydrophobic antioxidant can, in some embodiments, improve the stability of rapamycin in a bioactive agent delivery device.

The hydrophobic antioxidant(s) can be present in the polymer in an amount in the range of about 0.01 weight percent to about 10 weight percent of the total weight of the polymer, or in the range of about 0.5 weight percent to about 2 weight percent.

In some embodiments, one or more polymers comprising the biodegradable composition can optionally include one or more hydrophobic molecules. For example, when the polyetherester material includes a hydrophilic small-size drug (for example an aminoglycoside such as gentamycin), the biodegradable composition can also include, in addition to or instead of the hydrophobic antioxidant herein described, at least one hydrophobic molecule such as cholesterol, ergosterol, lithocholic acid, cholic acid, dinosterol, betuline, and/or oleanolic acid. One or more hydrophobic molecules can act to retard the release rate of the bioactive agent from the polyetherester copolymer. Such hydrophobic molecules can prevent water penetration into the biodegradable composition, but do not compromise the degradability of the biodegradable composition. In addition, such molecules have melting points in the range of 150°C to 200°C or more. Therefore, a small percentage of these molecules increase the T_g of the polymer, which decreases the

matrix diffusion coefficient for the bioactive agent to be released. Thus, such hydrophobic molecules can provide for a more sustained release of a bioactive agent from the biodegradable composition.

The hydrophobic molecule(s) can be present in the polymer in an amount in the range of about 0.1 weight percent to about 20 weight percent, or about 1 weight percent to about 5 weight percent, based upon the total weight of the polymer.

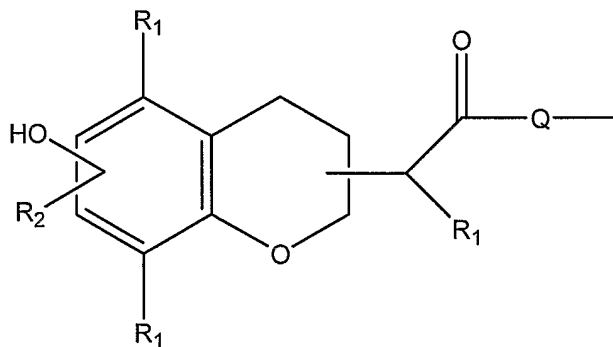
When the polyetherester copolymer contains a protein, the copolymer can also optionally include a hydrophilic antioxidant. Examples of hydrophilic antioxidants include, but are not limited to, those having the following structural formula XXXIII:

10



wherein each of Y and Z is 0 or 1, wherein at least one of Y and Z is 1. Each of X₁ and X₂ is independently selected from the group consisting of compounds of the formula XXXIV:

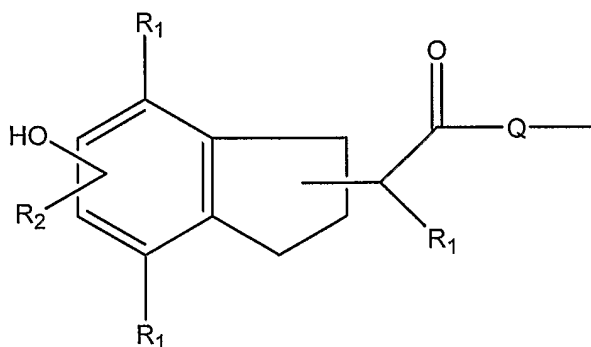
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and

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XXXIV

wherein each R_1 is hydrogen or an alkyl group having 1 to 4 carbon atoms, preferably methyl, and each R_1 is the same or different. R_2 is hydrogen or an alkyl group having 1 to 4 carbon atoms, preferably methyl. Q is NH or oxygen. Each of X_1 and X_2 can be the same or different. A is:



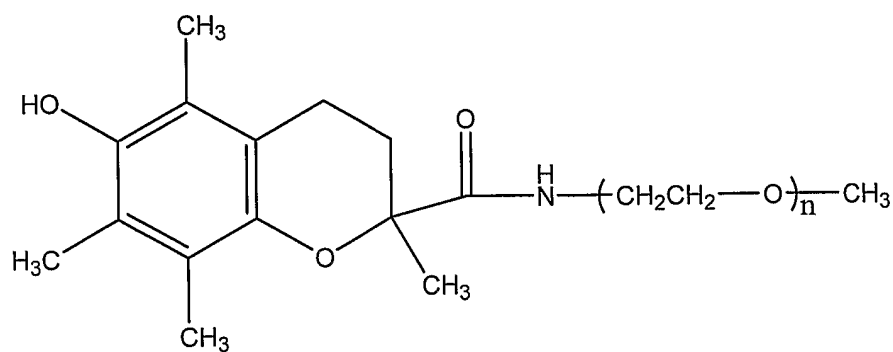
wherein R_3 is an alkyl group having 1 or 2 carbon atoms, preferably 2 carbon atoms; n is 1 to 100, preferably from 4 to 22; R_4 is an alkyl group having 1 to 4 carbon atoms, preferably 1 or 2 carbon atoms.

In one embodiment, one of Y and Z is 1, and the other of Y and Z is 0. In another embodiment, each of Y and Z is 1.

In yet another embodiment, R_3 is ethyl.

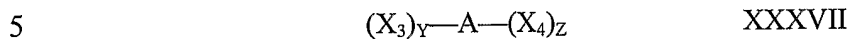
15 In a further embodiment, R_4 is methyl or ethyl.

In yet another embodiment, R_1 is methyl, R_2 is methyl, R_3 is ethyl, R_4 is methyl, one of Y and Z is 1 and the other of Y and Z is 0, Q is NH, n is 21 or 22, and the antioxidant has the following structural formula XXXVI:

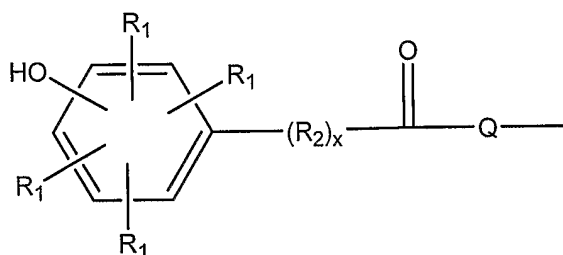


XXXVI

In another embodiment, the hydrophilic antioxidant has the following structural formula:



wherein each of Y and Z is 0 or 1, wherein at least one of Y and Z is 1. Each of X₃ and X₄ is:



10

XXXVIII

wherein each R₁ is hydrogen or an alkyl group having 1 to 4 carbon atoms, R₂ is an alkyl group having 1 to 4 carbon atoms, x is 0 or 1, and Q is NH or oxygen. Each R₁ is the same or different, and each of the X₃ and X₄ is the same or different. A is:



wherein R_3 is an alkyl group having 1 or 2 carbon atoms, preferably 2 carbon atoms; n is from 1 to 100, preferably from 4 to 22; and R_4 is an alkyl group having 1 to 4 carbon atoms, preferably 1 or 2 carbon atoms.

5 In one embodiment, at least one, preferably two, of the R_1 moieties is a tert-butyl moiety. When two of the R_1 moieties are tert-butyl moieties, each tert-butyl moiety is preferably adjacent to the —OH group.

The hydrophilic antioxidant(s) can be present in the polymer in an amount in the range of about 0.1 weight percent to about 10 weight percent, or about 1 weight percent to
10 about 5 weight percent, based upon the total weight of the polymer.

As discussed herein, one or more of the polymers comprising the biodegradable composition can include a hydrophobic antioxidant, hydrophobic molecule, and/or a hydrophilic antioxidant in the amounts described herein. The type and precise amount of antioxidant or hydrophobic molecule employed can be dependent upon the molecular
15 weight of the bioactive agent (protein), as well as properties of the polymer itself. If the polymer includes a large peptide or protein (such as, for example, insulin), the matrix can also optionally include a hydrophilic antioxidant such as those described herein and in the amounts described herein, and can also include polyethylene glycol having a molecular
20 weight in the range of about 1,000 to about 4,000, in an amount in the range of about 1 weight percent to about 10 weight percent, based upon the total weight of the copolymer.

In some embodiments, one or more polymers comprising the biodegradable composition can further include imaging materials. For example, materials can be included in the biodegradable composition to assist in medical imaging of the device once implanted. Medical imaging materials are well known. Exemplary imaging materials include
25 paramagnetic material, such as nanoparticulate iron oxide, Gd, or Mn, a radioisotope, and non-toxic radio-opaque markers (for example, caged barium sulfate and bismuth trioxide).

This can be useful for detection of medical devices that are implanted in the body (that are emplaced at the treatment site) or that travel through a portion of the body (that is, during implantation of the device). Paramagnetic resonance imaging, ultrasonic imaging, or other suitable detection techniques can detect such coated medical devices. In another example, 5 microparticles that contain a vapor phase chemical can be used for ultrasonic imaging. Useful vapor phase chemicals include perfluorohydrocarbons, such as perfluoropentane and perfluorohexane, which are described in U.S. Patent No. 5,558,854 (Issued 24 September, 1996); other vapor phase chemicals useful for ultrasonic imaging can be found in U.S. Patent No. 6,261,537 (Issued 17 July, 2001).

10 In some aspects, one or more polymers comprising the biodegradable composition can include an excipient. A particular excipient can be selected based upon its melting point, solubility in a selected solvent (such as a solvent that dissolves the polymer and/or the bioactive agent), and the resulting characteristics of the composition. Excipients can 15 comprises a few percent, about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, or higher percentage of the particular polymer in which it is included.

Buffers, acids, and bases can be incorporated in the polymer or polymers to adjust their pH. Agents to increase the diffusion distance of bioactive agents released from the polymer matrix can also be included. Illustrative excipients include salts, PEG or hydrophilic polymers, and acidic compounds.

20 Thus, additives can be included in one or more polymers comprising the biodegradable composition to assist in controlling release of bioactive agent, impacting degradation of the biodegradable composition, and/or impacting imaging of the device once 25 implanted.

Release of bioactive agent can also be impacted by modification of the polymers 25 comprising the biodegradable composition. Another technique for impacting release of bioactive agent can involve modifying the configuration of the device.

Optionally, the copolymer itself can be modified to affect the degradation rate and release rate of a bioactive agent. These aspects are particularly useful in embodiments comprising PEGT/PBT. For example, the copolymer can be modified by replacing components (monomeric units) with a particular hydrophobicity with a component
5 (monomeric unit) that has a differing hydrophobicity.

In some embodiments, the configuration of the device can be manipulated to control release of the bioactive agent. For example, the surface area and/or size of the device can be manipulated to control dosage of the bioactive agent(s) provided to the implantation site.

The composition of the copolymer and/or the device configuration can be modified
10 whether additives are included in the copolymer or not.

Preferably, the biodegradable composition is applied to selected surfaces of a medical device, such as a stent, wherein the stent itself is fabricated from a different material. The biodegradable composition coating can comprise a first polymer that is preferably a polyether ester copolymer, such as PEGT/PBT, and a second polymer selected
15 as described herein. Other polymers containing ester linkages that are suitable first biodegradable polymers are described herein.

In preferred aspects, the invention provides compositions and methods for providing biodegradable coatings containing bioactive agent to medical devices. The invention can be utilized in connection with medical devices having a variety of biomaterial surfaces.
20 Illustrative biomaterials include metals and ceramics. The metals include, but are not limited to, titanium, Nitinol, stainless steel, tantalum, and cobalt chromium. A second class of metals includes the noble metals such as gold, silver, copper, and platinum iridium. Alloys of metals are suitable for biomaterials as well. The ceramics include, but are not limited to, silicon nitride, silicon carbide, zirconia, and alumina, as well as glass, silica, and
25 sapphire.

Other illustrative biomaterials include those formed of synthetic polymers, including oligomers, homopolymers, and copolymers resulting from either addition or condensation polymerizations. Examples of suitable addition polymers include, but are not limited to, acrylics such as those polymerized from methyl acrylate, methyl methacrylate, hydroxyethyl methacrylate, hydroxyethyl acrylate, acrylic acid, methacrylic acid, glyceryl acrylate, glyceryl methacrylate, methacrylamide, and acrylamide; vinyls such as ethylene, propylene, vinyl chloride, vinyl acetate, vinyl pyrrolidone, and vinylidene difluoride. Examples of condensation polymers include, but are not limited to, nylons such as polycaprolactam, polylauryl lactam, polyhexamethylene adipamide, and polyhexamethylene dodecanediamide, and also polyurethanes, polycarbonates, polyamides, polysulfones, poly(ethylene terephthalate), polylactic acid, polyglycolic acid, polydimethylsiloxanes, and polyetherketone.

Certain natural materials are also suitable biomaterials, including human tissue such as bone, cartilage, skin and teeth; and other organic materials such as wood, cellulose, compressed carbon, and rubber.

Combinations of ceramics and metals are another class of biomaterials. Another class of biomaterials is fibrous or porous in nature. The surface of such biomaterials can be pretreated (for example, with a Parylene coating composition) in order to alter the surface properties of the biomaterial, when desired.

The coatings of the invention are applied to a surface in a manner sufficient to provide a suitably durable and adherent coating on the surface. Typically, the coatings are provided in a manner such that they are not chemically bound to the surface. Rather, the coatings can be envisioned as encapsulating the device surface. Given the nature of the association between the coating and surface, it will be readily apparent that the coatings can be applied to virtually any surface material to provide a suitably durable and adherent coating. Moreover, in some embodiments, a suitable surface pretreatment can be utilized, to

enhance the association between the coating and the device surface. For example, the device substrate surface may be roughened, or given a surface texture, by utilizing techniques (such as abrasion or micro-abrasion) well known in the art.

In some embodiments, the biodegradable composition is spray coated onto a surface of an implantable device, as described in the Examples herein. In other embodiments, the stent can be immersed in a biodegradable composition solution. Alternatively, the biodegradable composition can be extruded in the form of a tube that is then codrawn over a tube of stainless steel or Nitinol. By codrawing two tubes of the biodegradable composition over the metal tube, one positioned about the exterior of the metal tube and another positioned within such metal tube, a tube having multi-layered walls can be formed. Subsequent perforation of the tube walls to define a preselected pattern of spines and struts can impart the desired flexibility and expandability to the tube to create a stent.

The inventive biodegradable compositions can be applied to any desired portion of the device surface. For example, in some embodiments, the biodegradable composition coating can be provided on the entire surface of the device. In other embodiments, only a portion of the device can include the biodegradable composition coating. The portion of the device carrying the biodegradable composition coating can be selected based upon such factors as the application of the device, the amount of bioactive agent to be applied at a treatment site, the number and types of bioactive agents to be delivered, and like factors.

Moreover, each coated layer of the biodegradable composition can be provided on the surface of the device in any number of applications. The number of applications can be selected to provide individual coated layers of suitable thickness, as well as a desired total number of multiple coated layers of biodegradable composition, as desired. In such embodiments, the composition of individual layers of the coating can be the same or different, as desired. In some embodiments, the number of applications can be controlled to provide a desired overall thickness to the polymer coating. Generally, the thickness of the

coating is selected so that it does not significantly increase the profile of the device for implantation and use within a patient. Typically, the overall thickness of the biodegradable composition coating is on the order of about 1 μm to about 100 μm .

While multiple layers of coating composition can be applied to a single device when
5 desired, the invention can provide advantages through the ability to utilize a single coated layer that comprises a blend of two or more polymers. For example, a blend of first polymer, second polymer and bioactive agent can be applied as a single coated layer providing a desired release profile of bioactive agent. Illustrative embodiments of such
10 single coating layer aspects are included in the examples. In these aspects, the invention can provide devices and methods that include a minimum number of processing steps, since multiple coating layers are not required. This can reduce or eliminate the need for such steps as multiple application/purging steps when different coating compositions are to be applied from a single coating device, and/or multiple curing or drying steps, if such steps are desirable between coating layers.

15 The biodegradable composition can be applied as a blended polymer coating on any device that is introduced temporarily or permanently into a mammal for the prophylaxis or therapy of a medical condition. These devices include any that are introduced subcutaneously, percutaneously, or surgically to rest within an organ, tissue, or lumen of an organ, such as arteries, veins, ventricles, or atrium of the heart.

20 Biodegradable compositions of the invention can be used to coat the surface of a variety of implantable devices, for example: drug-delivering vascular stents (e.g., self-expanding stents typically made from nitinol, balloon-expanded stents typically prepared from stainless steel); other vascular devices (e.g., grafts, catheters, valves, artificial hearts, heart assist devices); implantable defibrillators; blood oxygenator devices (e.g., tubing,
25 membranes); surgical devices (e.g., sutures, staples, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular

implants, tissue adhesives and sealants, tissue scaffolds); membranes; cell culture devices; chromatographic support materials; biosensors; shunts for hydrocephalus; wound management devices; endoscopic devices; infection control devices; orthopedic devices (e.g., for joint implants, fracture repairs); dental devices (e.g., dental implants, fracture repair devices), urological devices (e.g., penile, sphincter, urethral, bladder and renal devices, and catheters); colostomy bag attachment devices; ophthalmic devices; glaucoma drain shunts; synthetic prostheses (e.g., breast); intraocular lenses; respiratory, peripheral cardiovascular, spinal, neurological, dental, ear/nose/throat (e.g., ear drainage tubes); renal devices; and dialysis (e.g., tubing, membranes, grafts).

10 Examples of useful devices include urinary catheters (e.g., surface-coated with antimicrobial agents such as vancomycin or norfloxacin), intravenous catheters (e.g., treated with antithrombotic agents (e.g., heparin, hirudin, coumadin), small diameter grafts, vascular grafts, artificial lung catheters, atrial septal defect closures, electro-stimulation leads for cardiac rhythm management (e.g., pacemaker leads), glucose sensors (long-term and short-term), degradable coronary stents (e.g., degradable, non-degradable, peripheral), blood pressure and stent graft catheters, birth control devices, benign prostate and prostate cancer implants, bone repair/augmentation devices, breast implants, cartilage repair devices, dental implants, implanted drug infusion tubes, intravitreal drug delivery devices, nerve regeneration conduits, oncological implants, electrostimulation leads, pain management implants, spinal/orthopedic repair devices, wound dressings, embolic protection filters, abdominal aortic aneurysm grafts, heart valves (e.g., mechanical, polymeric, tissue, percutaneous, carbon, sewing cuff), valve annuloplasty devices, mitral valve repair devices, vascular intervention devices, left ventricle assist devices, neuro aneurysm treatment coils, neurological catheters, left atrial appendage filters, hemodialysis devices, catheter cuff, 25 anastomotic closures, vascular access catheters, cardiac sensors, uterine bleeding patches,

urological catheters/stents/implants, in vitro diagnostics, aneurysm exclusion devices, and neuromodulators.

Examples of other suitable devices include, but are not limited to, vena cava filters, urinary dialators, endoscopic surgical tissue extractors, atherectomy catheters, clot
5 extraction catheters, percutaneous transluminal angioplasty catheters, PTCA catheters, stylets (vascular and non-vascular), coronary guidewires, drug infusion catheters, esophageal stents, circulatory support systems, angiographic catheters, transition sheaths and dialators, coronary and peripheral guidewires, hemodialysis catheters, neurovascular
10 balloon catheters, tympanostomy vent tubes, cerebro-spinal fluid shunts, defibrillator leads, percutaneous closure devices, drainage tubes, thoracic cavity suction drainage catheters, electrophysiology catheters, stroke therapy catheters, abscess drainage catheters, biliary drainage products, dialysis catheters, central venous access catheters, and parental feeding catheters.

Examples of medical devices suitable for the present invention include, but are not
15 limited to catheters, implantable vascular access ports, blood storage bags, vascular stents, blood tubing, arterial catheters, vascular grafts, intraaortic balloon pumps, cardiovascular sutures, total artificial hearts and ventricular assist pumps, extracorporeal devices such as blood oxygenators, blood filters, hemodialysis units, hemoperfusion units, plasmapheresis units, hybrid artificial organs such as pancreas or liver and artificial lungs, as well as filters
20 adapted for deployment in a blood vessel in order to trap emboli (also known as “distal protection devices”).

In some aspects, the polymeric compositions can be utilized in connection with ophthalmic devices. Suitable ophthalmic devices in accordance with these aspects can provide bioactive agent to any desired area of the eye. In some aspects, the devices can be
25 utilized to deliver bioactive agent to an anterior segment of the eye (in front of the lens),

and/or a posterior segment of the eye (behind the lens). Suitable ophthalmic devices can also be utilized to provide bioactive agent to tissues in proximity to the eye, when desired.

In some aspects, the polymeric compositions can be utilized in connection with ophthalmic devices configured for placement at an external or internal site of the eye.

5 Suitable external devices can be configured for topical administration of bioactive agent. Such external devices can reside on an external surface of the eye, such as the cornea (for example, contact lenses) or bulbar conjunctiva. In some embodiments, suitable external devices can reside in proximity to an external surface of the eye.

Devices configured for placement at an internal site of the eye can reside within any
10 desired area of the eye. In some aspects, the ophthalmic devices can be configured for placement at an intraocular site, such as the vitreous. Illustrative intraocular devices include, but are not limited to, those described in U.S. Patent Nos. 6,719,750 B2 ("Devices for Intraocular Drug Delivery," Varner et al.) and 5,466,233 ("Tack for Intraocular Drug Delivery and Method for Inserting and Removing Same," Weiner et al.); U.S. Publication
15 Nos. 2005/0019371 A1 ("Controlled Release Bioactive Agent Delivery Device," Anderson et al.), 2004/0133155 A1 ("Devices for Intraocular Drug Delivery," Varner et al.), 2005/0059956 A1 ("Devices for Intraocular Drug Delivery," Varner et al.), and 2003/0014036 A1 ("Reservoir Device for Intraocular Drug Delivery," Varner et al.); and
20 U.S. Application Nos. 11/204,195 (filed August 15, 2005, Anderson et al.), 11/204,271 (filed August 15, 2005, Anderson et al.), 11/203,981 (filed August 15, 2005, Anderson et al.), 11/203,879 (filed August 15, 2005, Anderson et al.), 11/203,931 (filed August 15, 2005, Anderson et al.), 11/225,301 (filed September 12, 2005, Anderson et al.); and related applications.

In some aspects, the ophthalmic devices can be configured for placement at a
25 subretinal area within the eye. Illustrative ophthalmic devices for subretinal application include, but are not limited to, those described in U.S. Patent Publication No. 2005/0143363

(“Method for Subretinal Administration of Therapeutics Including Steroids; Method for Localizing Pharmacodynamic Action at the Choroid and the Retina; and Related Methods for Treatment and/or Prevention of Retinal Diseases,” de Juan et al.); U.S. Application No. 11/175,850 (“Methods and Devices for the Treatment of Ocular Conditions,” de Juan et al.);
5 and related applications.

Suitable ophthalmic devices can be configured for placement within any desired tissues of the eye. For example, ophthalmic devices can be configured for placement at a subconjunctival area of the eye, such as devices positioned extrasclerally but under the conjunctiva, such as glaucoma drainage devices and the like.

10 The compositions are particularly useful for those devices that will come in contact with aqueous systems, such as bodily fluids. Such devices are coated with a coating composition adapted to release bioactive agent in a prolonged and controlled manner, generally beginning with the initial contact between the device surface and its aqueous environment. It is important to note that the local delivery of combinations of bioactive
15 agents may be utilized to treat a wide variety of conditions utilizing any number of medical devices, or to enhance the function and/or life of the device. Essentially, any type of medical device may be coated in some fashion with one or more bioactive agents that enhances treatment over use of the singular use of the device or bioactive agent.

In one preferred embodiment, the coating composition can also be used to coat
20 stents, e.g., either self-expanding stents, which are typically prepared from nitinol, or balloon-expandable stents, which are typically prepared from stainless steel. Other stent materials, such as cobalt chromium alloys, can be coated by the coating composition as well.

Devices which are particularly suitable include vascular stents such as self-
25 expanding stents and balloon expandable stents. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to

Wallsten and 5,061,275 issued to Wallsten et al. Examples of suitable balloon-expandable stents are shown in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco and U.S. Pat. No. 4,886,062 issued to Wiktor.

Optionally, the surface of some biomaterials can be pretreated (e.g., with a Parylene
5 TM coating composition) in order to alter the surface properties of the biomaterial. Parylene
CTM is the polymeric form of the low-molecular-weight dimer of para-chloro-xylylene.
Supplied by Specialty Coating Systems (Indianapolis), a Parylene CTM coating can be
deposited as a continuous coating on a variety of medical device parts to provide an evenly
distributed, transparent coating. This deposition is accomplished by a process termed vapor
10 deposition polymerization, in which dimeric Parylene CTM composition is vaporized under
vacuum at 150°C, pyrolyzed at 680°C to form a reactive monomer, then pumped into a
chamber containing the component to be coated at 25°C. At the low chamber temperature,
the monomeric xylylene is deposited on the part, where it immediately polymerizes via a
free-radical process.

15 Deposition of the xylylene monomer takes place in only a moderate vacuum (0.1
torr) and is not line-of-sight. That is, the monomer has the opportunity to surround all sides
of the part to be coated, penetrating into crevices or tubes and coating sharp points and
edges, creating what is called a "conformal" coating. Other illustrative priming materials
include silane, siloxane, polyurethane, polybutadiene, and polycarbodiimide.

20 When multiple coated layers are applied to form the coating, each coating layer is
applied sequentially and without intermediate curing or laminating steps. Typically, the
individual polymer layers are simply dried between applications. Preferably, the coated
layers adhere to the device surface and to each other without requiring any heating, pressure,
or other treatment steps that could impact the stability of the bioactive agents and/or the
25 polymer components of the coating. Surprisingly, the coated layers provide substantially
durable coatings on device surfaces without requiring such treatments.

In use, the implantable device is placed within a patient at a desired implantation site. Upon contact with body fluids, the body fluids initially permeate at least a portion of the biodegradable composition, allowing for dissolution and diffusion of the bioactive agent from the biodegradable composition. The biodegradable composition undergoes gradual
5 degradation (usually primarily through hydrolysis) with concomitant release of the dispersed bioactive agent for a sustained or extended period. This can result in prolonged delivery of therapeutically effective amounts of the bioactive agent.

In preferred aspects, the biodegradable composition includes polymers that are surface erodible and bulk erodible biodegradable materials. Surface erodible materials are
10 materials in which bulk mass is lost primarily at the surface of the material that is in direct contact with the physiologic environment, such as body fluids. Bulk erodible materials are materials in which bulk mass is lost throughout the mass of the material; in other words, loss of bulk mass is not limited to mass loss that occurs primarily at the surface of the material in direct contact with the physiological environment.

15 In preferred aspects, the biodegradable composition is composed of only biodegradable polymers. In other words, the components of the biodegradable composition are selected to be broken down by the body over time.

Typically, current drug-eluting stents release anti-restenosis agent over a period of four (4) or more weeks. In preferred aspects, the inventive biodegradable compositions can
20 provide a controlled release of bioactive agent to thereby provide a therapeutically effective dose of the bioactive agent for a sufficient time to provide the intended benefits. The controlled release includes both an initial release and subsequent sustained-release of the bioactive agent.

In preferred aspects, the inventive biodegradable compositions provide coatings that
25 demonstrate excellent uniformity and durability during use. Coating uniformity and durability can be observed and assessed as follows.

One aspect of coating uniformity relates to surface features of the coating. The inventive coatings can be examined for uniformity and defects using a Field Emission Scanning Electron Microscope (SEM) at a low beam voltage (1 kV) which allows detailed imaging of surface features. Illustrative surface defects can include areas of delamination or cracking of the coating, surface areas that lack one or more coated layers, and the like. An overall survey of the coating quality is made at low magnification, and when features of interest are identified, higher magnification images are taken. From the overall survey, a qualitative ranking of the relative amount and type of defects in the coatings can be made.

Another aspect of coating uniformity relates to the uniformity of mixing of bioactive agent into the biodegradable compositions. This aspect of the coatings can be imaged using a confocal scanning Raman microscope. Laser light (532 nm wavelength) is focused onto the coating via a 100x microscope objective (numerical aperture 0.95), and the coating is scanned in three directions using a piezoelectric transducer driven platter. The scattered light from the coating is collected by the microscope, filtered, split into its spectrum using a spectrograph, and detected with a CCD detector. Thus, for each position (pixel) in the image, a Raman spectrum is measured. Reference spectra of the pure bioactive agent and pure polymer are incorporated into an augmented classical least squares analysis to create separate images of bioactive agent only and polymer only. These images are overlapped to create a composite color coded image of the distribution of bioactive agent within the polymer.

Uniformity of bioactive agent distribution within the coatings can impact the release profile of the bioactive agent. If a large percentage of the bioactive agent is concentrated at a particular portion of the coating, the release of the bioactive agent is less likely to exhibit controlled release kinetics. For example, if a large percentage of bioactive agent is concentrated at the surface of a coated layer, the bioactive agent is more likely to be released quickly from the coated layer, since the bioactive agent does not have a large

diffusion distance to the surface. In contrast, a bioactive agent that is concentrated towards the device surface may have a larger diffusion distance to travel, and thus release of the bioactive agent may be delayed relative to the prior exemplary coating. Moreover, concentration of a bioactive agent within a coating can result in a release profile that

5 includes one or more sudden increases in release, as polymer degradation reaches the area of bioactive agent concentration.

As used herein, the term “durability” refers to the ability of a coating to adhere to a device surface when subjected to forces typically encountered during use (for example, normal force, shear force, and the like). A more durable coating is less easily removed from

10 a substrate by abrasion or compression. Durability of a coating can be assessed by subjecting the device to conditions that simulate use conditions. To simulate use of the coated devices, the coated stents are placed over sample angioplasty balloons. The stent is then crimped onto the balloon using a laboratory test crimper (available from Machine Solutions, Brooklyn, NY). The stent and balloon are then placed in a water bath having a

15 temperature of 37°C. After 5 minutes of soaking, the balloon is expanded using air at 5 atmospheres (3800 torr) of pressure. The balloon is then deflated, and the stent is removed. The stent is then examined by optical and scanning electron microscopy to determine the amount of coating damage caused by cracking and/or delamination. Herein, this durability testing will be referred to as the “Mechanical Testing.” Coatings with extensive damage are

20 considered unacceptable for a commercial medical device. Testing can be followed up with contact angle testing, staining in Toluidine Blue solution (Aldrich, Milwaukee, Wis.), and/or SEM analysis to visualize the coating adherence to the substrate.

For purposes of illustrating the inventive concepts herein, the present discussion has focused on providing the biodegradable compositions in the form of a coating on a surface

25 of a device. However, given the present description, one of skill in the relevant art would readily appreciate that the biodegradable compositions can be utilized to form a structural

component of the device itself. In these aspects, then, any selected component of the device structure can be fabricated of the biodegradable compositions of the invention, as desired.

The invention will now be described with reference to the following non-limiting examples.

5

Examples

The following procedures and materials were used for the Examples.

For the examples, three multiblock copolymers of poly(ethylene glycol)terephthalate/poly(1,4-butylene)terephthalate (PEGT/PBT) were obtained from OctoPlus, B.V. Leiden, The Netherlands. These polymers are referred to as PolyActive™ and had the following properties:

10

PEGT/PBT wt. ratio	PEG average molecular weight (g/mol)	Nomenclature
55/45	300	300PEGT55PBT45
80/20	1000	1000PEGT80PBT20
55/45	1000	1000PEGT55PBT45

Poly(L-Lactide) with a weight-average molecular weight 100,000-150,000 and an inherent viscosity of 0.90-1.20 dL/g was used without further purification. Poly(DL-Lactide) with a weight-average molecular weight 75,000-120,000 and an inherent viscosity of 0.55-0.75 dL/g was used without further purification. Poly(DL-Lactide-co-Glycolide) with a weight-average molecular weight 50,000-75,000 and a composition of 50 mole percent of each monomer was used without further purification. These polymers are referred to as PLLA, PDLLA, and PLGA, respectively. All three polymers were purchased from Sigma-Aldrich (St. Louis, USA).

15

20

Poly(L-lactide-co-caprolactone-co-glycolide) [P(LLA-CL-GLA)] was obtained from Sigma-Aldrich (St. Louis, USA; Product No. 568562, average M_w approximately 100,000 by GPC, L-lactide 70%).

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Poly[(lactide-co-ethyleneglycol)-co-ethoxyphosphate] was obtained from Sigma-Aldrich (St. Louis, USA; Product No. 659606).

Dexamethasone ("Dexa") was purchased from Sigma Aldrich (St. Louis, USA) and was 98% pure.

5 Paclitaxel ("PTX") was purchased from LC Laboratories (Division of PKC Pharmaceuticals, Inc., Woburn, MA) and was greater than 99% pure.

Surface pretreatment by application of Parylene CTM coating

For all of the Examples, stents were first provided with a priming coated layer of Parylene CTM. The Parylene CTM coating was accomplished by a process termed vapor
10 deposition polymerization, in which dimeric Parylene CTM composition was vaporized under vacuum at 150°C, pyrolyzed at 680°C to form a reactive monomer, then pumped into a chamber containing the component to be coated at 25°C. At the low chamber temperature, the monomeric xylylene was deposited on the part, where it immediately polymerized via a free-radical process. The polymer coating reached molecular weights of approximately 500
15 kilodaltons.

Deposition of the xylylene monomer took place in only a moderate vacuum (0.1 torr) and was not line-of-sight. That is, the monomer had the opportunity to surround all sides of the part to be coated, penetrating into crevices or tubes and coating sharp points and edges, creating what is called a "conformal" coating.

20 Preparation of Coated Layers Containing PolyActiveTM Polymer

For preparation of polymer coating compositions including dexamethasone, the dexamethasone was first dissolved in THF and then added to a polymer/chloroform solution. Each PolyActiveTM polymer was dissolved into chloroform with dexamethasone. The concentration of PolyActiveTM polymer was 27 milligram per milliliter while
25 concentration of dexamethasone was 3 milligram per milliliter. The resulting solution was agitated at 25°C until there was no evidence by visible inspection of insoluble material.

Preparation of PLLA Coatings

For preparation of polymer coating compositions including dexamethasone, the dexamethasone was first dissolved in THF and then added to a polymer/chloroform solution. The PLLA polymer was dissolved into chloroform with dexamethasone. The
5 concentration of polymer was 27 milligram per milliliter while the concentration of dexamethasone was 3 milligram per milliliter. The resulting solution was agitated at 25°C until there was no evidence by visible inspection of insoluble material.

Coating Procedure

Each coating solution was applied to commercially available stainless steel stents
10 (for example, Laserage Technology Corporation, IL) using an ultrasonic spray head connected to a syringe pump. See U.S. Patent Application Publication No. US 2004/0062875 A1 (Chappa et al., "Advance Coating Apparatus and Method," April 1, 2004). After coating, the stents were placed under vacuum to remove the solvent. Typical coating weights on each stent were approximately 500 micrograms after drying, unless
15 indicated specifically to the contrary.

Bioactive Agent Elution Experiments

The following elution experiments were utilized for coatings containing dexamethasone. Before and after stent coating, each stent was weighed to measure the amount of coating on the stent. Bioactive agent release was measured in phosphate-buffered
20 saline (PBS, pH 7.4) or 0.45% Tween Acetate Buffer (TAB, in distilled water). In a typical procedure, each stent was placed in a 5-milliliter amber scintillation vial. A magnetic stir bar and 4 milliliters of PBS buffer (1 liter water, 9 grams sodium chloride, 0.27 grams potassium phosphate monobasic (KH_2PO_4), and 1.4 grams potassium phosphate dibasic (K_2HPO_4)) was added to each of the vials. The vials were placed in a 37°C water bath. At
25 each sampling time (usually 4 or 5 times on the first day followed by daily sampling thereafter), the stent was removed and placed in fresh buffer solution in a new vial.

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Concentration of bioactive agent (dexamethasone) at each sampling time was determined in the spent buffer by UV spectroscopy using the characteristic wavelength for each bioactive agent. This concentration was converted to a mass of bioactive agent released from the coating using molar absorptivities.

5 For assays utilizing TAB, 4 milliliters of TAB buffer (1 liter water, 0.704 g sodium acetate, and 1.6 ml 1M acetic acid, and 4.05 ml Tween 80) was added to each of the vials. The vials were placed in a 37°C water bath. At each sampling time, the stent was removed and placed in fresh buffer solution in a new vial, as described for the PBS elution assay. Concentration of bioactive agent at each sampling time was determined in the spent buffer
10 by HPLC.

The cumulative mass of the released bioactive agent was calculated by adding the individual sample mass after each removal. The release profile was obtained by plotting the amount of released bioactive agent as a function of time.

Once the elution experiment was finished, the stents were dried overnight in a
15 vacuum oven set at room temperature (25- 27°C) and weighed to ensure the accuracy of the UV spectroscopy results.

For coatings containing paclitaxel, the following procedures were followed to observe bioactive agent elution. Paclitaxel content and quality from coated stent samples were analyzed by immersing the paclitaxel coated stents into a glass test tube filled with 2.5
20 to 4 ml 0.1%acetic acid in MeOH, which dissolves coated material, including paclitaxel, from the cobalt chromium stent surface. The tube was capped, covered with aluminum foil and shaken for 3 hours using a mechanical shaker. After shaking, the solution was filtered via a 0.45 micron Nylon Acrodisc syringe filter (having the extracted paclitaxel) and was analyzed by HPLC using the following parameters:

25 HPLC column = ODS Hypersil C18, 150 x 4.6 mm, 5 u particle size
Column temp = 35 deg C

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Mobile phase = 50:50 acetonitrile/water

Flow rate = 1.2 ml/min

Injection volume = 10 ul

Rinse solution = 80:20 acetonitrile/water

5 UV Detection wavelength = 227 nm

Run time = 10 min

The HPLC column was equilibrated with the mobile phase solution (50:50 acetonitrile/water) and tested using a paclitaxel standard, which produces a peak for paclitaxel at 227 nm. In order to determine the amount of paclitaxel (μg) content in the stent coating, 3 paclitaxel standard solutions were run in duplicate. The average peak area of each standard was used to generate a calibration curve (Peak area vs concentration in $\mu\text{g}/\text{ml}$). Next, test samples (0.1%AA/MeOH with paclitaxel extracted from coated stents) were run on the HPLC. The PTX concentration (in $\mu\text{g}/\text{ml}$) was determined from the standard curve and multiplied by the volume of 0.1%AA/MeOH to determine amount (in μg) of paclitaxel extracted from the coated stents.

Example 1 – Elution of Bioactive Agent from Unblended PolyActive™ and PLLA Coatings Including a Single Coated Layer

To establish baseline elution profiles, coating compositions including PLLA with dexamethasone, and PolyActive™ polymer with dexamethasone, were prepared as described previously. The coating solutions were applied to the stents as described previously. The coating weights for each composition, as well as the amount of dexamethasone contained in each formulation, were approximately equivalent.

Results are shown in Table 2 and Figure 1. Table 2 lists the coating and bioactive agent weights. Dexamethasone elution results from the coatings of Table 2 are shown in Figure 1.

Table 2 – Coating Characteristics - Unblended

Coating	First Layer Polymer	First Layer Weight (μg)	Second Layer Weight (μg)	Dexamethasone Weight (μg)
A	PLLA/Dexa	486	N/A	54
B	1000PEGT80PBT20/D exa	521	N/A	52

As shown in the Figure 1, coatings comprised of unblended PolyActive™ polymer released dexamethasone relatively quickly. The coating comprised of unblended PolyActive™ polymer (Coating B) showed a substantial burst (greater than 90% of bioactive agent) within the first day. In contrast, coatings composed of a single coated layer composed of PLLA released dexamethasone much more slowly due to the hydrophobicity of PLLA (Coating A). No burst was observed with the single coated layer of PLLA. The difference in release rates from the two polymers is due to the hydrophilic portions of the polymer allowing water penetration and rapid drug diffusion for Coating B, versus the relatively hydrophobic nature of PLLA (Coating A).

The observed release profiles can be explained as follows. Dexamethasone has a relatively low molecular weight (MW = 392) and thus diffuses through a polymer matrix more easily than larger molecular weight bioactive agents. Release of dexamethasone from PolyActive™ polymer (Coating B) showed a substantial burst (greater than 90% of drug). The PolyActive™ coatings released dexamethasone quickly due to the hydrophilic portions of the polymer allowing water penetration and rapid drug diffusion (Coating B). In contrast, PLLA released dexamethasone much more slowly due to its hydrophobicity (Coating A).

Given the duration of the experiments (approximately 16 days), release of dexamethasone was primarily due to diffusion of the bioactive agent through the polymer matrix, and not by degradation of the matrix.

Example 2 – Elution of Bioactive Agent from Representative Blended Coatings

5 Including PEGT/PBT Copolymer and PLLA

Representative blended biodegradable compositions were prepared to include a model small molecular weight drug (dexamethasone). The resulting biodegradable compositions were provided on the surface of stents and tested for elution of the bioactive agent as follows.

10 To prepare blended biodegradable compositions, solutions of PolyActive™ copolymer, PLLA, and dexamethasone were each dissolved in chloroform to a total solids concentration of 30 mg/ml. These solutions were applied to The stents as described previously.

The ratio of PolyActive™ copolymer to PLLA was varied to demonstrate the
15 adjustment of the dexamethasone elution rate from each stent. Table 3 lists the coating compositions, and Figure 2 shows the elution rate results for the blended coatings.

Table 3 – Coating Characteristics

Coating	Coating Composition	Weight Percent PolyActive to PLLA	Coating Weight (µg)	Dexamethasone Weight, (µg)
M	1000PEGT80PBT20/PLLA	33/67%	490	49
N	1000PEGT80PBT20/PLLA	11/89	443	44
O	1000PEGT80PBT20/PLLA	6/94	466	47

As illustrated in Figure 2, results indicated that inclusion of higher ratios of
20 PolyActive™ copolymer in the biodegradable compositions increased the initial release rate of the bioactive agent from the blended coating compositions. Coating M demonstrated a pronounced initial burst release of dexamethasone. This pronounced burst can be attributed

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to the dissolution of dexamethasone through the biodegradable composition. The initial burst release phase accounted for essentially 100% of the drug (taking into account experimental error) contained in the biodegradable composition. In contrast, Coatings N and O (containing lower ratios of PolyActive™ copolymer) demonstrated a marginal initial release rate (approximately 10% for Coating N and less than 10% for Coating O), followed by substantially zero order release profiles.

The observed release profiles can be discussed as follows. The PolyActive™ component of the coatings is relatively more hydrophilic than the PLLA component. Thus, by modifying the ratio of these two components, the burst release was controlled. The coating that included relatively less PLLA (Coating M) exhibited a substantial burst release. As the amount of PLLA was increased in the coating compositions, the burst release was substantially reduced. Thus, the amount of hydrophobic polymer can be selected to provide a desired initial burst, followed by a sustained release. Put another way, the amount of hydrophilic component (PolyActive™ polymer) of the coating can be modified to allow a desired amount of diffusion of aqueous fluids into the coating, thereby facilitating controlled diffusion of a bioactive agent from the coating composition. As the initial burst release is controlled, more of the bioactive agent will be available for subsequent treatment of the patient.

As the ratio of PLLA to PolyActive™ copolymer was increased, the release rate was decreased. This demonstrated that the drug elution rate can be adjusted by varying the polymer ratio. The incorporation of hydrophilic PolyActive™ copolymer can increase the degradation rate of PLLA.

Figure 2 also shows the cumulative percentage of released dexamethasone over time for the three different blended biodegradable compositions. Compared to coatings that included a higher amount of PolyActive™ copolymer, the blended compositions with relatively less PolyActive™ copolymer clearly demonstrated controlled release profiles.

For example, approximately 100% of the dexamethasone was released in the first hours from the Coating M. In comparison, blended coatings containing less PolyActive™ polymer and more PLLA released less than 20% (Coating N) and less than 10% (Coating O) of dexamethasone at 3.5 days.

5 **Example 3 – Elution of Bioactive Agent from Representative Blended Coatings
Including PEGT/PBT Copolymer and P(LLA-CL-GLA)**

Representative blended biodegradable compositions were prepared to include a model small molecular weight drug (paclitaxel). The resulting biodegradable compositions were provided on the surface of stainless steel stents and tested for elution of the bioactive
10 agent as follows. Stents were pretreated with Parylene™ (as described herein) prior to application of biodegradable coatings.

To prepare blended biodegradable compositions, solutions of PolyActive™ copolymer, P(LLA-CL-GLA), and paclitaxel were each dissolved in chloroform to a total solids concentration of 40 mg/ml. These solutions were applied to stents as described
15 previously.

The ratio of PolyActive™ copolymer to P(LLA-CL-GLA) was varied to demonstrate the adjustment of the PTX elution rate from each stent. Table 4 lists the coating compositions, and Figure 3 shows the elution rate results for the blended coatings.

Table 4 – Coating Characteristics

Coating	Polymer Composition	Weight Percent PTX/PolyActive/ P(LLA-CL- GLA)
11-13, 26	1000PEGT55PBT45/P(LLA-CL-GLA)	10/5/85
14, 15, 21, 22	1000PEGT55PBT45/P(LLA-CL-GLA)	10/20/70
23-25, 27	1000PEGT55PBT45/P(LLA-CL-GLA)	10/30/60

For each group of stents, two samples were subjected to elution studies, one sample was subjected to surface characterization (optical, Raman and SEM), and one sample was
5 subjected to mechanical studies.

Elution studies

In Figure 3, results indicated that inclusion of higher ratios of PolyActive™ copolymer in the biodegradable compositions increased the initial release rate of the bioactive agent from the blended coating compositions. Coatings 23 and 24 demonstrated a
10 pronounced initial burst release of paclitaxel. The initial burst release phase accounted for more than 90% of the drug (taking into account experimental error) contained in the biodegradable composition. In contrast, Coatings 11 and 12 (containing lower ratios of PolyActive™ copolymer) demonstrated a lower initial release rate (approximately 25% for Coating 11 and approximately 21% for Coating 12). By day 2 of the study, both Coatings
15 11 and 12 demonstrated controlled release profiles.

As discussed above regarding blends of PolyActive™ with PLLA, the PolyActive™ component of the coatings is relatively more hydrophilic than the P(LLA-CL-GLA) component. Thus, by modifying the ratio of these two components, the burst release was controlled. The coatings that included relatively less P(LLA-CL-GLA) (Coatings 23 and 24
20) exhibited a substantial burst release. As the amount of P(LLA-CL-GLA) was increased in

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the coating compositions, the burst release was substantially reduced. This supports the conclusion that the amount of hydrophobic polymer can be selected to provide a desired initial burst, followed by a sustained release. Again, the amount of hydrophilic component (PolyActive™ polymer) of the coating can be modified to allow a desired amount of
5 diffusion of aqueous fluids into the coating, thereby facilitating controlled diffusion of a bioactive agent from the coating composition. As discussed elsewhere herein, by controlling the initial burst release, more of the bioactive agent is available for sustained treatment of the patient.

Similar to the effects seen with PLLA above, as the ratio of P(LLA-CL-GLA) to
10 PolyActive™ copolymer was increased, the release rate was decreased. This demonstrated that the drug elution rate can be adjusted by varying the polymer ratio. The incorporation of hydrophilic PolyActive™ copolymer can increase the degradation rate of P(LLA-CL-GLA).

Figure 3 also shows the cumulative percentage of released paclitaxel over time for the three different blended biodegradable compositions. Compared to coatings that included
15 a higher amount of PolyActive™ copolymer, the blended compositions with relatively less PolyActive™ copolymer clearly demonstrated controlled release profiles. For example, approximately 93% of the paclitaxel was released in the first 24 hours from the Coatings 23 and 24. In comparison, blended coatings containing less PolyActive™ polymer and more P(LLA-CL-GLA) released less than 40% (Coating 11) and less than 43% (Coating 12) of
20 paclitaxel at 14 days.

Surface Characterization

Surface analysis of the samples was performed to characterize the polymer coating on the stents, observing coating quality, uniformity, and mixing of the components.

Optical and SEM images showed coatings on the metal stents had no webbing,
25 cracking or coating delamination. No crystals of the paclitaxel were seen in the optical or SEM images. Overall, coatings appeared uniform across each stent. Figures 5-7 show

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Optical images for Coatings 13, 22 and 25 (100X magnification). Figures 8-10 show SEM Images of the Coatings 13 (Figure 5), 22 (Figure 6), and 25 (Figure 7). SEM images showed that the coatings were quite smooth with little debris; no spray droplets were visible at the surface of Coating 13, while some spray droplets were visible at surfaces of Coatings
5 22 and 25.

Confocal Raman images showed the distribution of the coating components on each stent. Cross-sectional Raman images (taken perpendicular to the metal stent struts) were obtained over regions 50µm in width and 10 or 15 µm in depth. In a cross-sectional image, the air above the coating had no Raman signal, the coating had a strong Raman signal, and
10 the metal below the coating had no Raman signal.

At each pixel in the image, an entire Raman spectrum was obtained. An augmented classical least squares (CLS) algorithm was applied to deconvolute the data set into images of the individual components using reference spectra for P(LLA-CL-GLA), 1000PEGT55PBT45, 1000PETT80PBT20, paclitaxel, and parylene.

15 In all stents examined, the biodegradable polymers and the paclitaxel appeared to mix completely with no large segregations or drug crystals formed within the coatings. The images showed that the paclitaxel mixed into the biodegradable polymers uniformly, with no large phase segregation or crystals formed in the coatings. Further, no concentration of paclitaxel towards an area of the blended coating (e.g., the device surface or the outer
20 surface) was observed.

Mechanical Testing

After conventional balloon expansion of a selected stent, visual inspection of the stent coating under 6.3x magnification was conducted to determine coating quality on the stent. Inspection revealed that stent coatings with polymer blends comprising paclitaxel, PolyActive™ and P(LLA-CL-GLA) as a second polymer provided acceptable coatings.
25 Acceptable stent coatings were characterized in appearance, for example, by minimal

surface cracking, minimal webbing between stent struts, smooth texture to the coating surface, and coating adherence to the stent substrate.

Example 4 - Elution of Bioactive Agent from Representative Blended

Coatings Including PEGT/PBT Copolymer and P(LLA-EG-EOP)

5 Representative blended biodegradable compositions were prepared to include a model small molecular weight drug (paclitaxel). The resulting biodegradable compositions were provided on the surface of stainless steel stents and tested for elution of the bioactive agent as follows. Stents were pretreated with Parylene™ as described in Example 3.

To prepare blended biodegradable compositions, solutions of PolyActive™
10 copolymer, P(LLA-EG-EOP), and paclitaxel were each dissolved in chloroform to a total solids concentration of 40 mg/ml. These solutions were applied to stents as described previously.

The ratio of PolyActive™ copolymer to P(LLA-EG-EOP) was varied to demonstrate the adjustment of the PTX elution rate from each stent. Table 5 lists the
15 coating compositions, and Figure 4 shows the elution rate results for the blended coatings.

Table 5 – Coating Characteristics

Coating	Polymer Composition	Weight Percent PTX/PolyActive/ P(LLA-EG-EOP)
60-63	1000PEGT55PBT45/P(LLA-EG-EOP)	10/5/85
64-67	1000PEGT55PBT45/P(LLA- EG-EOP)	10/20/70
68-71	1000PEGT55PBT45/P(LLA- EG-EOP)	10/30/60

For each group of stents, two samples were subjected to elution studies, one sample was subjected to surface characterization (optical, Raman and SEM), and one sample was
20 subjected to mechanical studies.

Elution Studies

Results indicated that inclusion of higher ratios of PolyActive™ copolymer in the biodegradable compositions increased the initial release rate of the bioactive agent from the blended coating compositions. Coatings 64, 65, 68 and 69 demonstrated a pronounced
5 initial burst release of paclitaxel. The initial burst release phase accounted for more than 90% of the drug (taking into account experimental error) contained in the biodegradable composition. In contrast, Coatings 60 and 61 (containing lower ratios of PolyActive™ copolymer) demonstrated a lower initial release rate (approximately 34% for Coating 60 and approximately 35% for Coating 61), followed by controlled release profiles.

10 As discussed above regarding blends of PolyActive™ with PLLA, the PolyActive™ component of the coatings is relatively more hydrophilic than the P(LLA-EG-EOP) component. Thus, by modifying the ratio of these two components, the burst release was modified. The coatings that included relatively less P(LLA-EG-EOP) exhibited a substantial burst release; as the amount of P(LLA-EG-EOP) was increased in the coating
15 compositions, the burst release was substantially reduced. This supports the conclusion that the amount of hydrophobic polymer can be selected to provide a desired initial burst, followed by a sustained release.

Similar to the effects seen with PLLA above, as the ratio of P(LLA-EG-EOP) to PolyActive™ copolymer was increased, the release rate was decreased. This demonstrated
20 that the drug elution rate can be adjusted by varying the polymer ratio. Figure 4 also shows the cumulative percentage of released paclitaxel over time for the three different blended biodegradable compositions. Compared to coatings that included a higher amount of PolyActive™ copolymer, the blended compositions with relatively less PolyActive™ copolymer clearly demonstrated controlled release profiles. For example, blended coatings
25 containing less PolyActive™ polymer and more P(LLA-EG-EOP) released less than 35% (Coating 60) and less than 36% (Coating 61) of paclitaxel at 14 days.

Surface Characterization

Optical and SEM images showed coatings on the metal stents had no webbing, cracking or coating delamination. No crystals of the paclitaxel were seen in the optical or SEM images. Overall, coatings appeared uniform across each stent. Figures 11-13 show
5 Optical images for Coatings 62, 66 and 70, respectively (100X magnification). Figures 14-16 show SEM Images of the Coatings 62 (Figure 14), 66 (Figure 15), and 70 (Figure 16).

Confocal Raman images were taken as described in Example 3. In all stents examined, the biodegradable polymers and the paclitaxel appeared to mix completely with no large segregations or drug crystals formed within the coatings. The images showed that
10 the paclitaxel mixed into the biodegradable polymers uniformly, with no large phase segregation or crystals formed in the coatings. Further, no concentration of paclitaxel towards an area of the blended coating (e.g., the device surface or the outer surface) was observed.

Mechanical Testing

15 After conventional balloon expansion of a selected stent, visual inspection of the stent coating under 6.3x magnification was conducted to determine coating quality on the stent. Inspection revealed that stent coatings with polymer blends comprising paclitaxel, PolyActive™ and P(LLA-EG-EOP) as a second polymer provided acceptable coatings. Acceptable stent coatings were characterized in appearance, for example, by minimal
20 surface cracking, minimal webbing between stent struts, smooth texture to the coating surface, and coating adherence to the stent substrate.

Results of the various Examples indicate that adjustment of the ratio of PolyActive™ polymer to a more hydrophobic polymer can control the initial burst release and subsequent release rate of a relatively small molecular weight bioactive agent from
25 biodegradable coatings. Thus, both the initial release and subsequent sustained release (approximately zero-order release) can be precisely controlled by adjusting the relative

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amounts of PEGT/PBT polymer to relatively hydrophobic polymer (such as those illustrated in the Examples). Results of the Examples also demonstrate the ability to provide bioactive agent release profiles that include a linear release phase for extended periods of time. The inventive methods and devices thus provide the feature of tunability of bioactive agent
5 release rates from polymeric coating compositions.

In designing a coating that can provide controlled release of a bioactive agent, it is desirable to have the capability to modulate the shape of the release curve. The time profile of the release of the bioactive agent can range from immediate release where the drug elutes all at once (much like a step function) to an extremely slow, linear (zero order) release,
10 where the drug is evenly released over many months or years. Depending upon the drug and the condition being treated, there are a variety of release profiles that are of interest. The objective of creating coatings including blends of biodegradable polymers is to be able to attain the broad range of release profiles that lie between a step function and a low-slope, zero-order release.

15 One of the primary strategies to control the release of a bioactive agent, is to limit the initial release (or "burst") of bioactive agent. If this can be achieved, then more bioactive agent is available at later times for a more extended release duration. The inclusion of biodegradable coatings composed of blends of polymers described herein is designed to limit or even eliminate the burst of bioactive agent from the coating. The
20 bioactive agent still remaining in the coating after the initial burst is then released to the site of action over a longer time period. The shape of the release profile (percentage of drug released versus time) after the burst can be controlled to be linear or logarithmic or some more complex shape, again depending on the composition of the polymers comprising the blended system and bioactive agent in the coating.

25 Once a therapeutic range has been determined (for example, by a physician), the inventive coatings can be adjusted to provide the bioactive agent at a dosage that is within

the therapeutic range. The inventive compositions provide improved means to control release of the bioactive agent, thus providing enhanced ability to deliver bioactive agent at desired rates and amounts.

5 The results discussed in the preceding Examples show that the inventive blended biodegradable coating compositions can limit initial release of bioactive agent and provide control over the shape of the release profile curves.

Other embodiments of this invention will be apparent to those skilled in the art upon consideration of this specification or from practice of the invention disclosed herein. Various omissions, modifications, and changes to the principles and embodiments described
10 herein may be made by one skilled in the art without departing from the true scope and spirit of the invention which is indicated by the following claims. All patents, patent documents, and publications cited herein are hereby incorporated by reference as if individually incorporated.

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We claim:

1. An implantable medical article having a bioactive agent releasing coating, the coating comprising a blend of:
 - (a) a first biodegradable polymer that is a copolymer of polyalkylene glycol terephthalate and an aromatic polyester;
 - (b) a second biodegradable polymer; and
 - (c) bioactive agent,wherein the second biodegradable polymer is selected to have a slower bioactive agent release rate relative to the first biodegradable polymer.
2. The article according to claim 1 wherein the polyalkylene glycol terephthalate is selected from the group of polyethylene glycol terephthalate, polypropylene glycol terephthalate, polybutylene glycol terephthalate, and combinations of these.
3. The article according to claim 2 wherein the polyalkylene glycol is polyethylene glycol.
4. The article according to claim 1 wherein the polyester is selected from polyethylene terephthalate, polypropylene terephthalate, polybutylene terephthalate, and combinations of these.
5. The article according to claim 4 wherein the polyester is polybutylene terephthalate.
6. The article according to claim 1 wherein the first polymer is a copolymer of polyethylene glycol terephthalate and polybutylene terephthalate in relative amounts of 70-80% polyethylene glycol terephthalate and 5-20% polybutylene terephthalate.
7. The article according to claim 1 wherein the first biodegradable polymer is present in an amount in the range of 2-50% by weight, based upon total weight of the coating composition.

25

8. The article according to claim 1 wherein the second biodegradable polymer is more hydrophobic relative to the first biodegradable polymer.
9. The article according to claim 1 wherein the second biodegradable polymer comprises a polymer derived from monomers selected from lactic acid, glycolic acid, caprolactone, ethylene glycol, and ethyloxyphosphate.
5
10. The article according to claim 1 wherein the second biodegradable polymer comprises a blend of two or more poly(ester-amide) polymers.
11. The article according to claim 1 wherein the blend is a miscible blend of the first biodegradable polymer and the second biodegradable polymer.
- 10 12. The article according to claim 1 wherein the bioactive agent is a hydrophobic small molecule bioactive agent.
13. The article according to claim 12 wherein the bioactive agent has a molecular weight of 1500 or less.
14. The article according to claim 13 wherein the bioactive agent is selected from anti-proliferative agents, anti-inflammatory agents, immunosuppressive agents, small
15 molecule antibiotics, estrogens, and combinations of any of these.
15. The article according to claim 14 wherein the bioactive agent is selected from actinomycin D, paclitaxel, taxane, dexamethasone, prednisolone, tranilast, cyclosporine, everolimus, mycophenolic acid, sirolimus, tacrolimus, estradiol, and
20 combinations of any of these.
16. The article according to claim 1 wherein two or more bioactive agents are included in the coating.
17. The article according to claim 13 wherein upon placement of the article in a biological environment, the bioactive agent is released, and wherein release is 30%
25 or less within 24 hours after placement of the article in the biological environment.

18. The article according to claim 13 wherein the bioactive agent is released at a therapeutically effective concentration for at least one week, when the article is implanted in a patient.
19. The article according to claim 13 wherein the bioactive agent is released at a therapeutically effective concentration for at least 4 weeks, when the article is implanted in a patient.
20. The article according to claim 1 wherein the coating is provided on a surface of the article that comprises less than 100% of total article surface area.
21. The article according to claim 1 wherein the bioactive agent releasing coating further comprises a coating layer comprising parylene, silane, siloxane, polyurethane, polybutadiene, polycarbodiimide, or a mixture of any of these.
22. The article according to claim 1 wherein the article is a stent, graft, catheter, valve, cardiac device, ophthalmic device, or wound dressing.
23. A coating composition for coating an implantable medical article, the coating composition comprising a true solution of:
- (a) a first biodegradable polymer that is a copolymer of polyalkylene glycol terephthalate and an aromatic polyester;
 - (b) a second biodegradable polymer; and
 - (c) solvent.
24. The coating composition according to claim 23 further comprising bioactive agent.
25. A method for preparing an implantable medical article comprising steps of:
- (a) preparing a blend of at least two biodegradable polymers having distinct biodegradation rates,
 - (b) providing bioactive agent to the blend; and
 - (c) disposing the blend on a surface of an implantable medical article,

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wherein the blend comprises a polyether ester copolymer as a first biodegradable polymer, and a second biodegradable polymer that is selected to control release of the bioactive agent from the blend composition.

26. The method according to claim 25 wherein the step of providing bioactive agent to the blend is performed prior to disposing the blend on a surface of an implantable medical article.
27. A method of delivering bioactive agent to a patient in a controlled manner, the method comprising steps of providing the device according to claim 1 to a patient, and maintaining the device in the patient for a selected period of time, during which time the bioactive agent is released from the coating composition in a controlled manner.

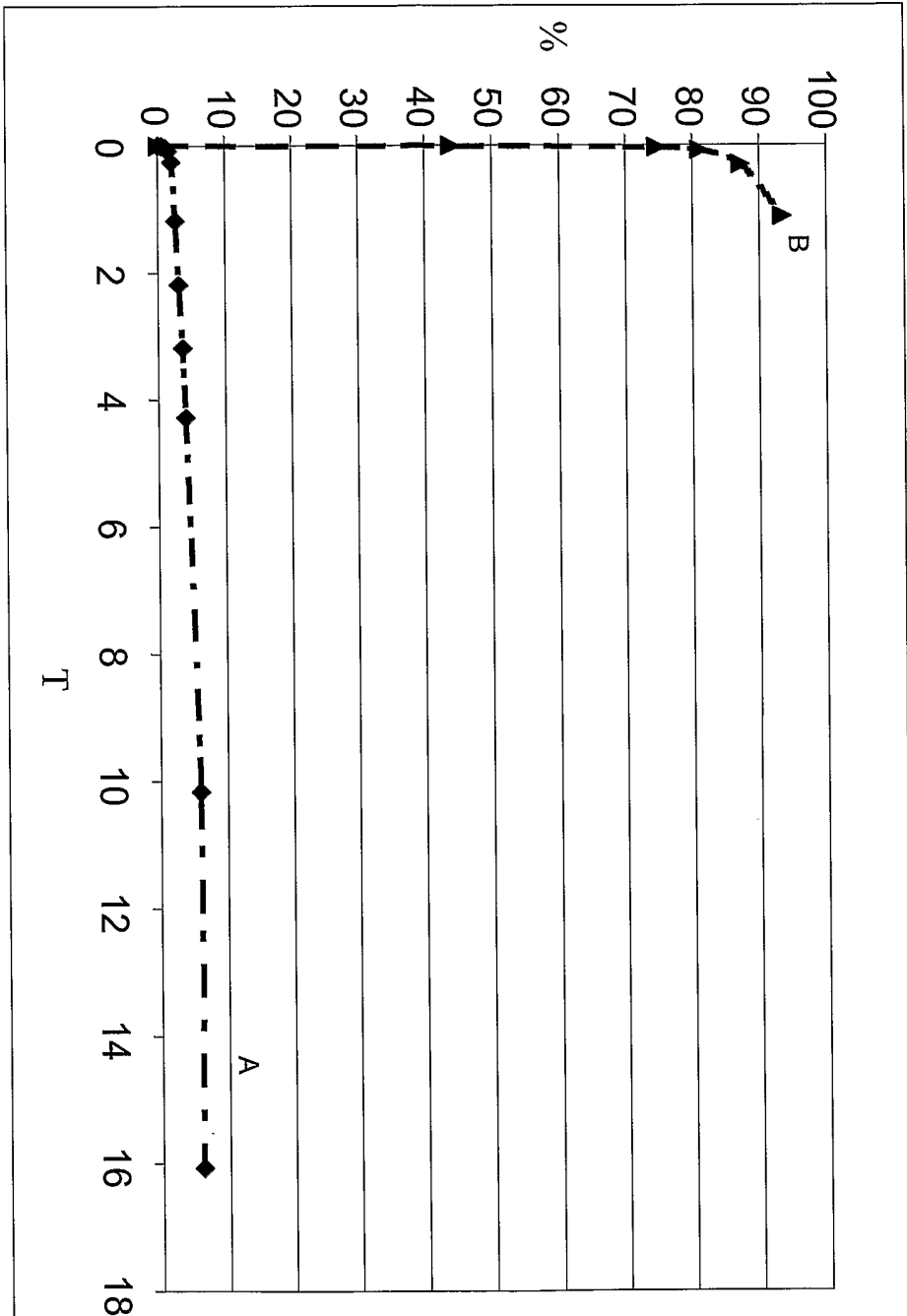


Figure 1

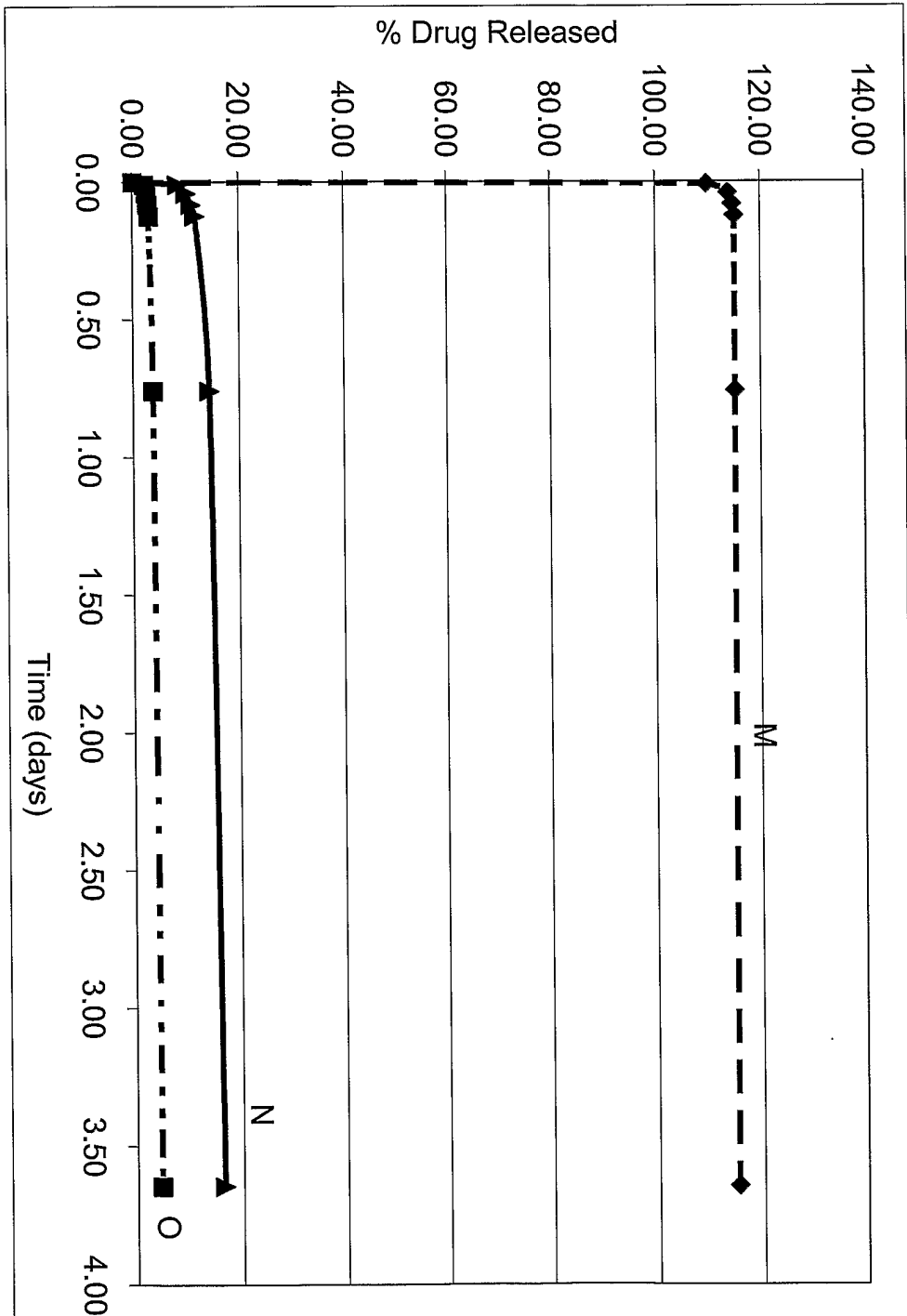


Figure 2

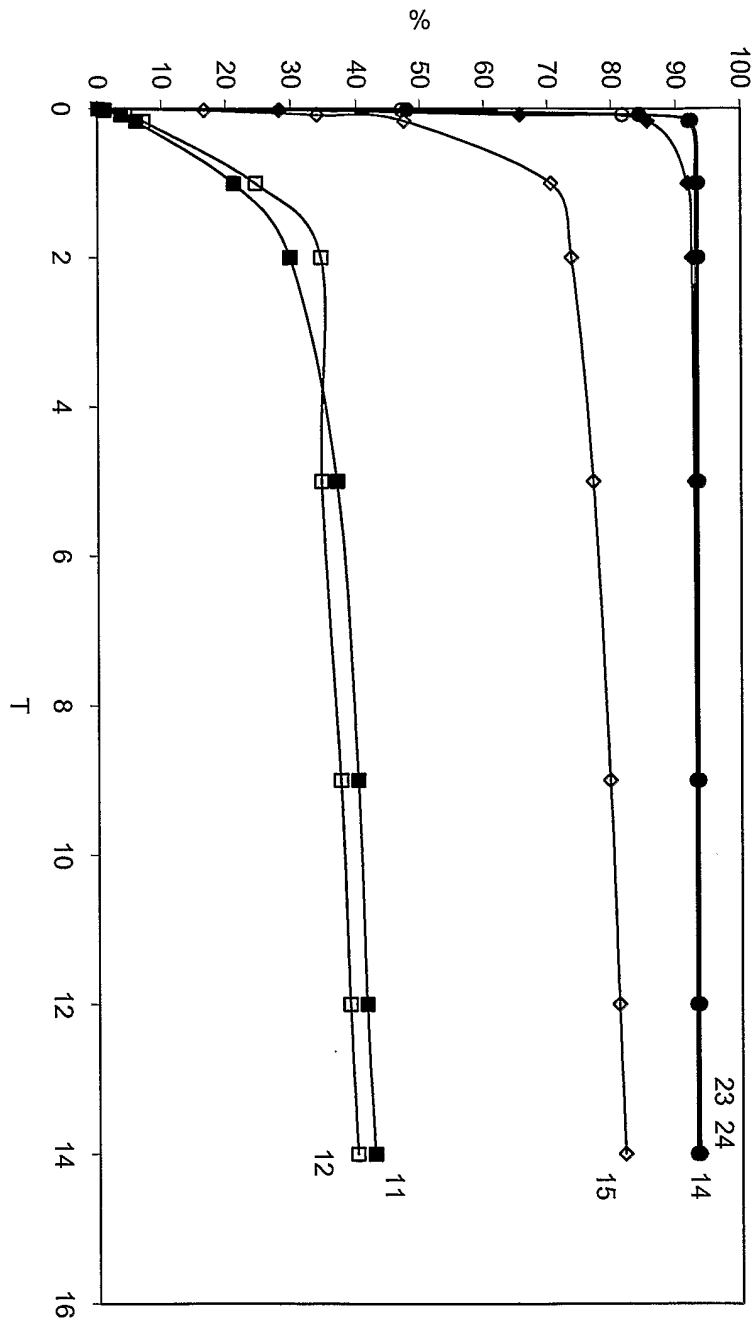


Figure 3

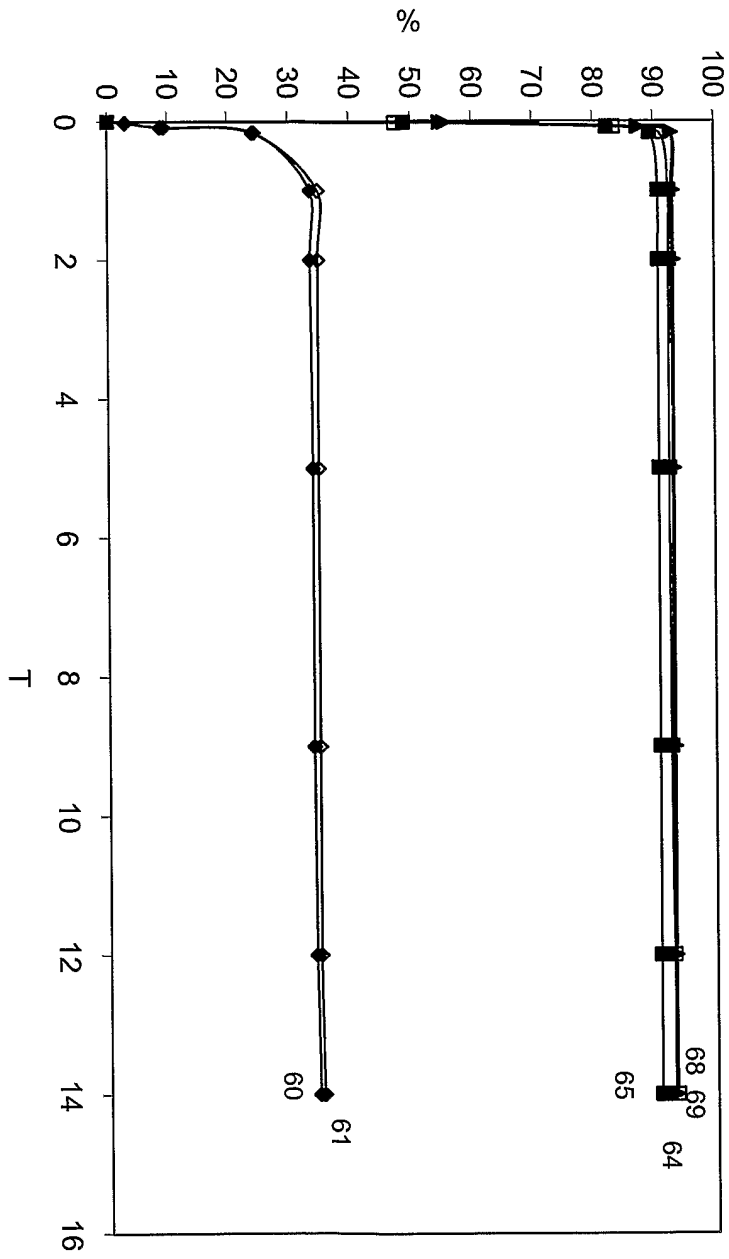


Figure 4



Figure 5



Figure 6

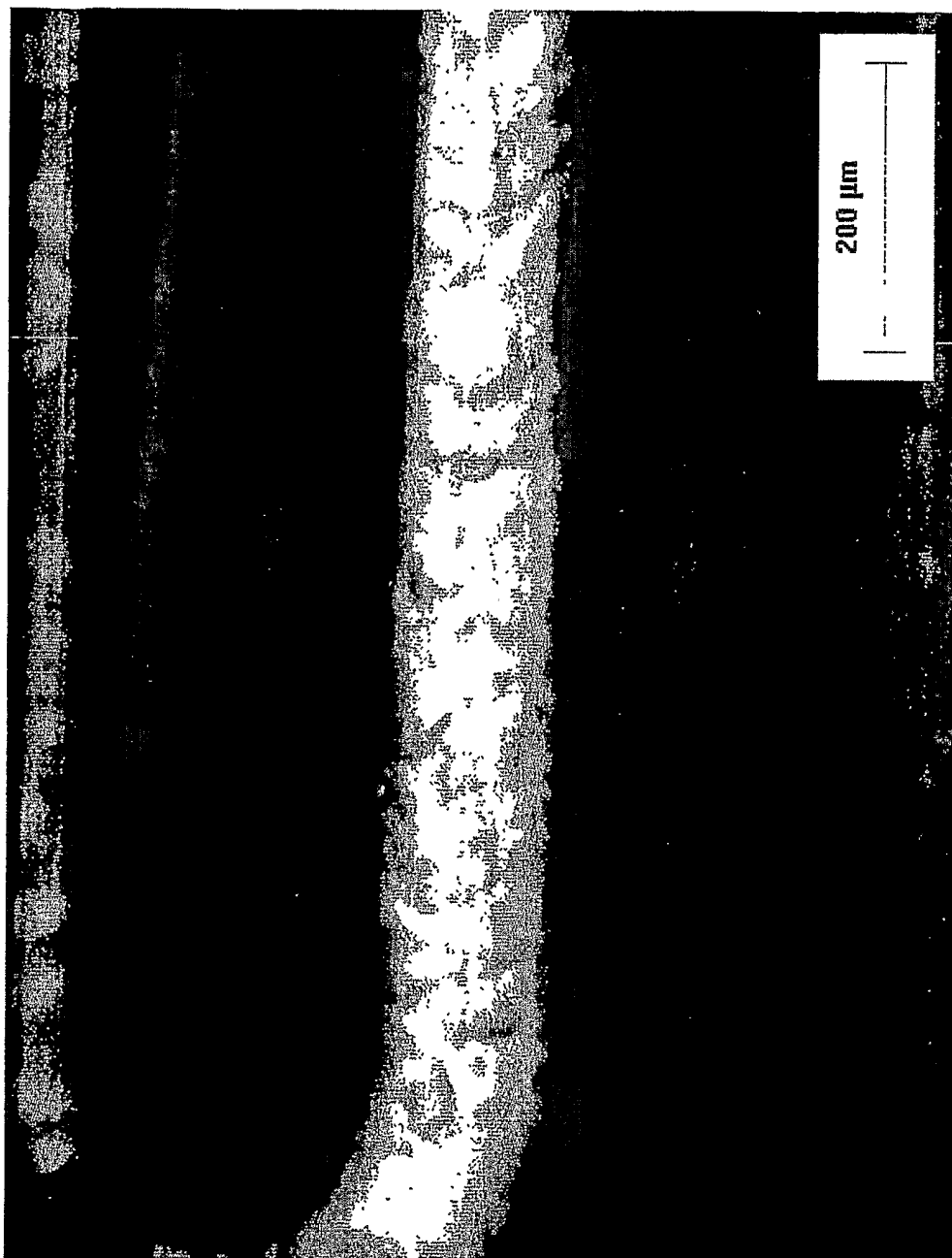


Figure 7

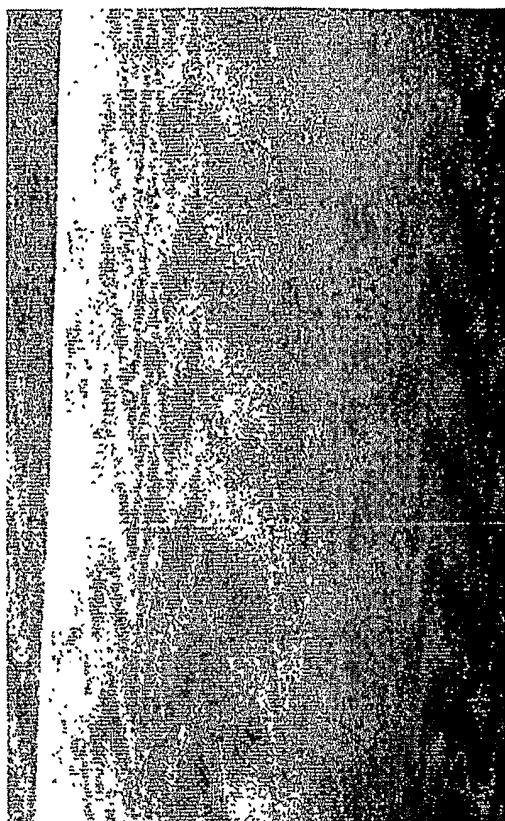


Figure 8

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Figure 9

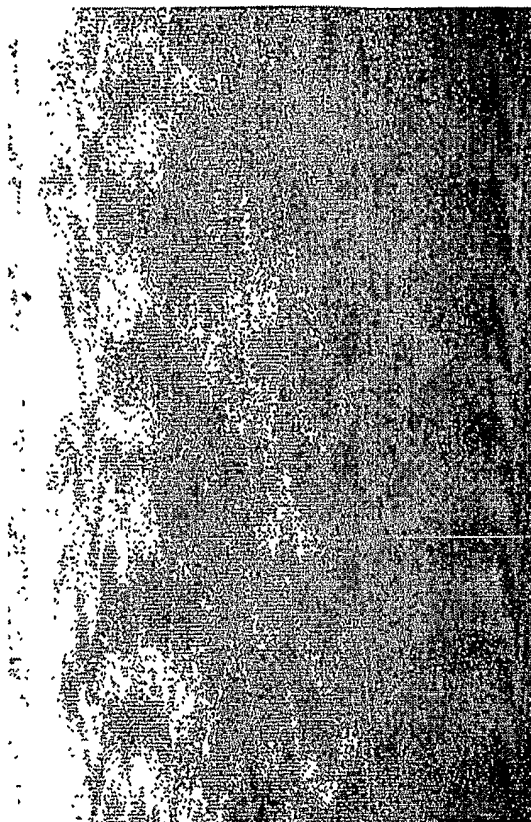


Figure 10

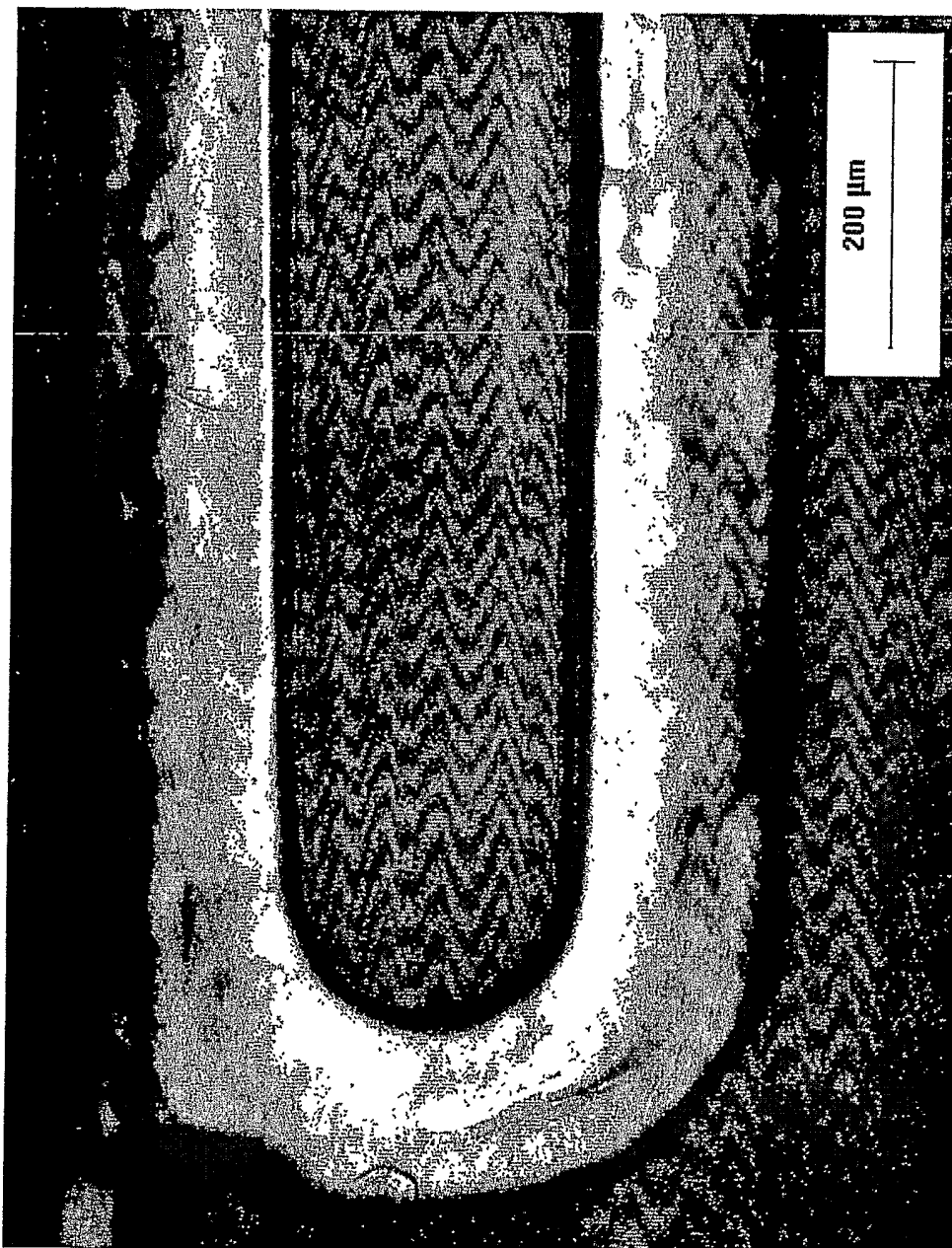


Figure 11

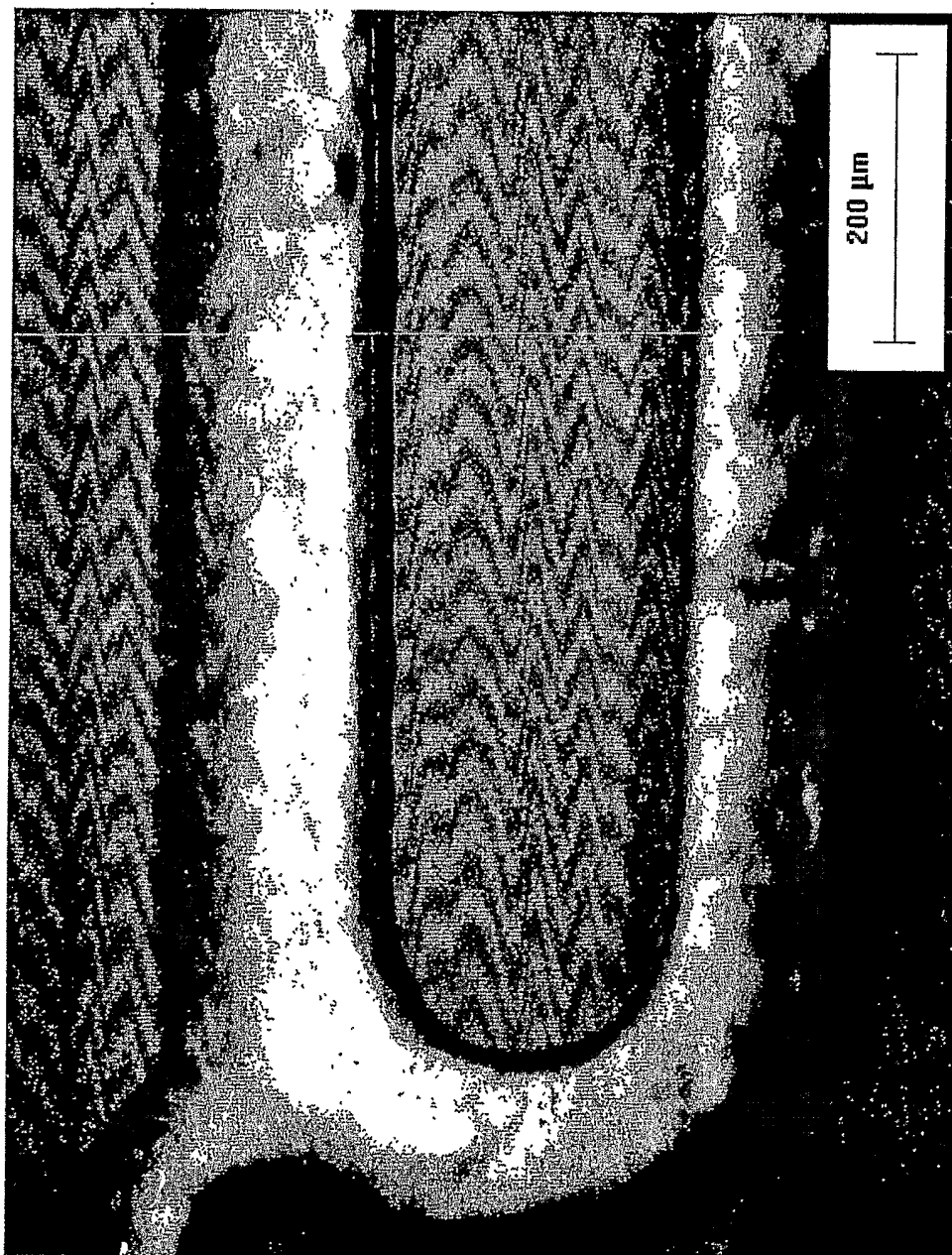


Figure 12

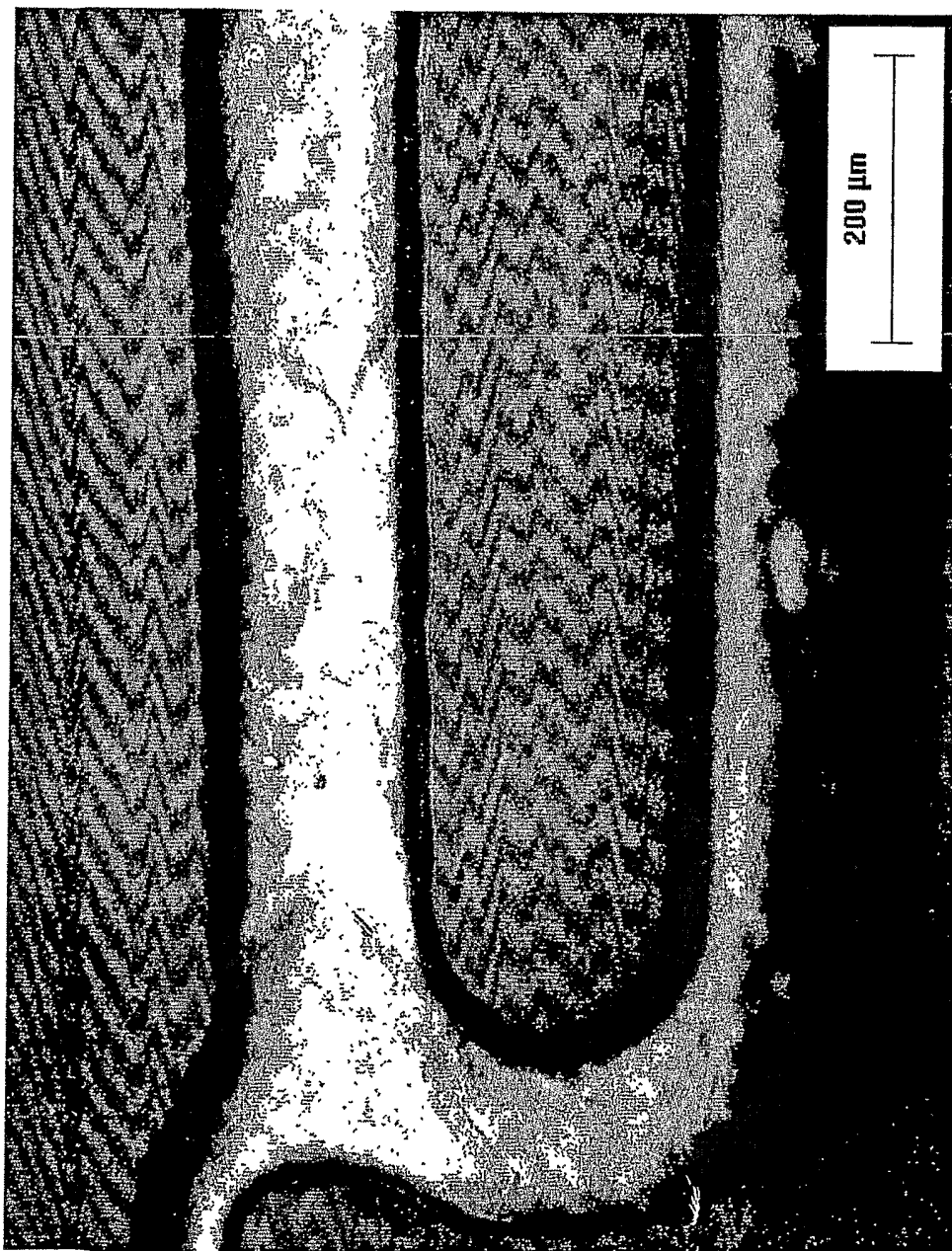


Figure 13

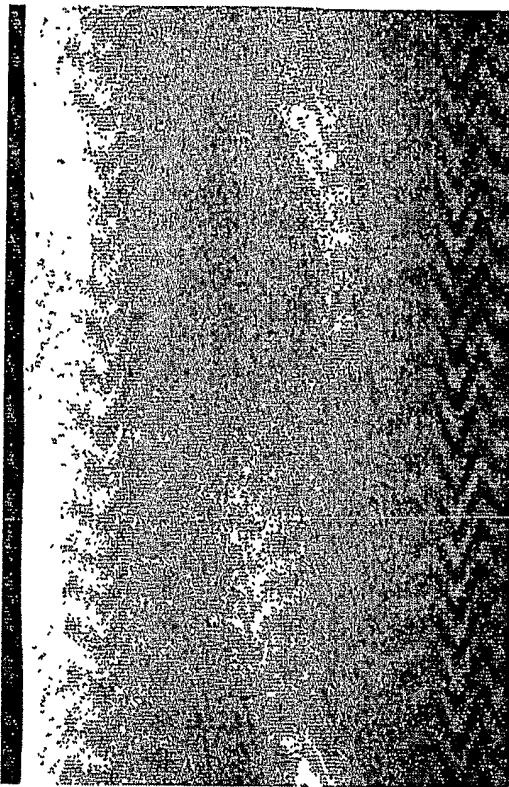


Figure 14



Figure 15

16/16

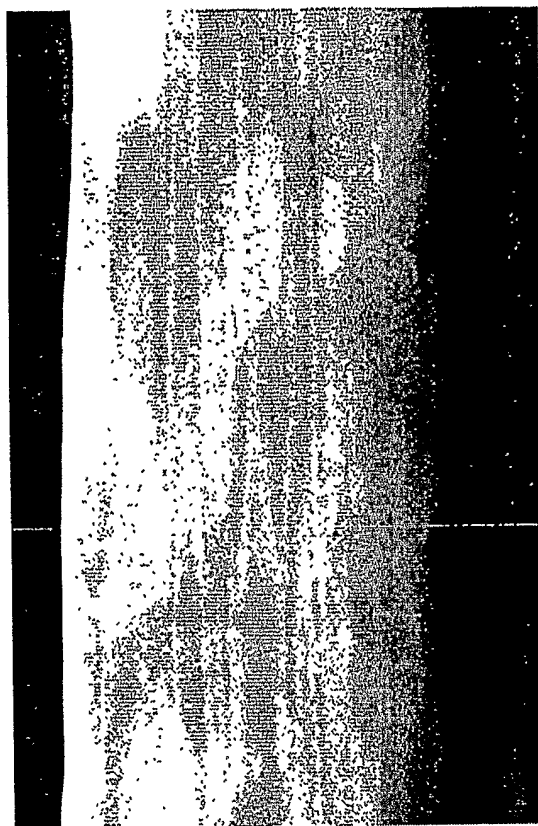


Figure 16

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