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(54) **BIODEGRADABLE HYDROPHOBIC POLYSACCHARIDE-BASED COATINGS**

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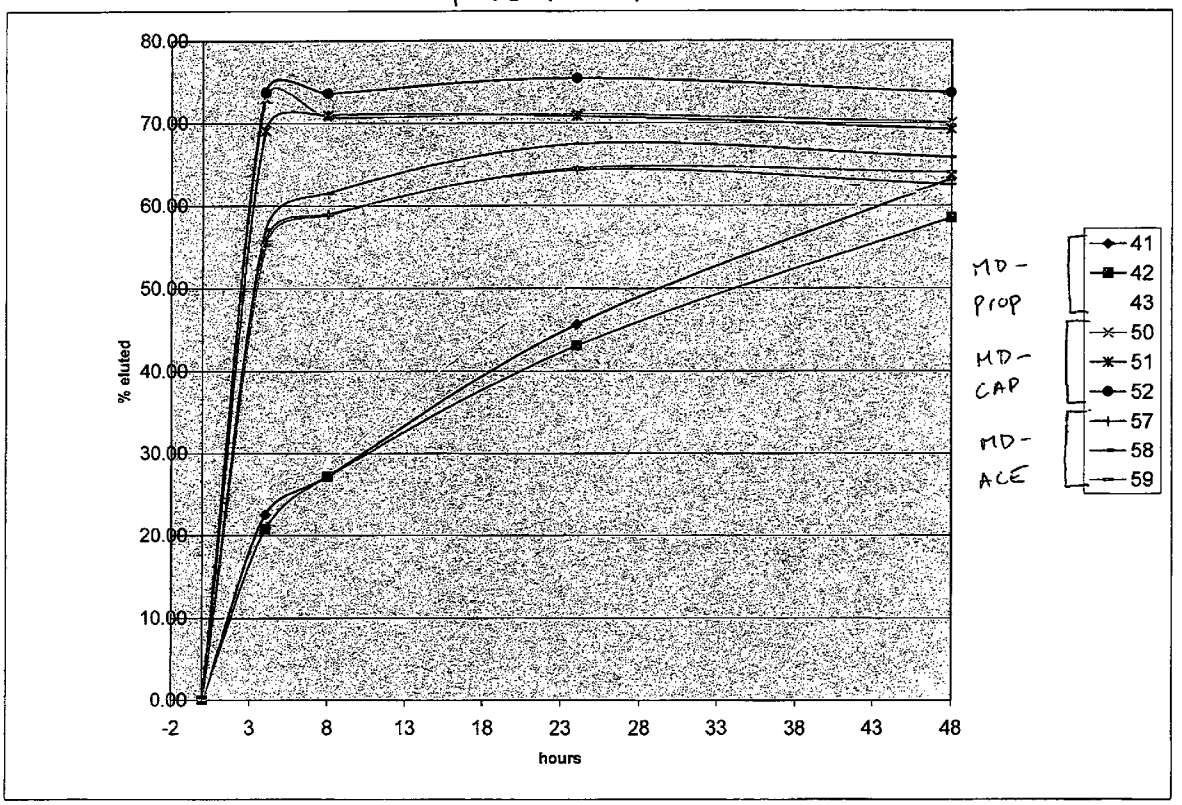
(57) **ABSTRACT**

Implantable medical articles having a coating formed of hydrophobic derivatives of natural biodegradable polysaccharides are described. The coatings can include a bioactive agent, and demonstrate desirable bioactive agent release profiles and can be prepared to have high drug loading. The coated implantable medical articles can be used to treat medical conditions, such as those requiring prolonged administration of the bioactive agent at a target location in the body.

FIGURE 1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BIODEGRADABLE HYDROPHOBIC POLYSACCHARIDE-BASED COATINGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present non-provisional Application claims the benefit of commonly owned provisional Application having Ser. No. 60/782,957, filed on Mar. 15, 2006, and entitled HYDROPHOBIC DERIVATIVES OF NATURAL BIODEGRADABLE POLYSACCHARIDES; and commonly owned provisional Application having Ser. No. 60/900,853, filed on Feb. 10, 2007, and entitled BIODEGRADABLE HYDROPHOBIC POLYSACCHARIDE-BASED DRUG DELIVERY IMPLANTS; which Applications are incorporated herein by reference in their entirety.

TECHNICAL FIELD

[0002] The present invention relates to biodegradable coatings for implantable medical articles. The method also relates to methods for treating medical conditions by releasing a bioactive agent from the coatings to a subject.

BACKGROUND

[0003] Coatings formed on the surface of medical devices have been shown to be beneficial as they can improve the properties of the device in one or more ways. As examples, coatings can provide the surface of implantable medical devices, such as catheters and stents, with lubricious, non-thrombogenic, biocompatible, and drug-delivery properties. Coatings providing one or more of these features can improve the function of the implanted device in the body.

[0004] Site-specific drug delivery can be accomplished by injection and/or implantation of an article or device that releases the drug to the treatment site. Injection of drugs can have limitations, for example, by requiring multiple administrations, increasing risk of complications (such as infection), and patient discomfort. Implantation of a coated article or device that delivers drug to the treatment site via the coating has therefore gained much interest in recent years.

[0005] For example, stents have been prepared with non-biodegradable coatings that include anti-proliferative compounds. These compounds can be released from the stents surface and minimizes the accumulation of smooth muscle cells on the stent surface, thereby providing an anti-restenotic effect.

[0006] Generally speaking, a bioactive agent can be coupled to the surface of a medical device by surface modification, embedded, and released from within polymeric materials (matrix-type), or surrounded by and released through a carrier (reservoir-type). The polymeric 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, a greater percentage of coating exposed on the medical device, and the thickness of the polymer coating can contribute to adverse reactions to the medical device.

[0007] Drug-releasing biodegradable coatings formed from polylactic acid have been used to coat medical device surfaces (see, for example, U.S. Pat. No. 6,258,121). As the coating degrades, the bioactive agent is released from the surface of the device. These types of biodegradable materials, however, have the potential to degrade into products that cause unwanted side effects in the body by virtue of their presence or concentration in vivo. These unwanted side effects can include immune reactions, toxic buildup of the degradation products in the body, or the initiation or provocation of other adverse effects on cells or tissue in the body. If materials that are used to prepare the implant promote an adverse tissue response in the body, the effectiveness of the implant can be reduced.

[0008] Several other challenges confront the use of medical devices or articles that release bioactive agents into a patient's body. For example, treatment may require release of the bioactive agent(s) over an extended period of time (for example, weeks, months, or even years), and it can be difficult to sustain the desired release rate of the bioactive agent(s) over such long periods of time.

[0009] While advances in site-specific implantable drug delivery systems have been made, many systems do not release drug in a desired manner following implantation in a patient. For example, in many systems the majority of the drug present in the article is released from the device in an initial burst, resulting in premature depletion of the drug. Following this depletion, the drug may be delivered to the subject in sub-optimal amounts.

[0010] In other systems, such as those based on polylactide-type biodegradable polymers, the majority of drug may be released at later points during the administration period due to bulk erosion of the drug containing biodegradable matrices.

[0011] If drug is prematurely released from the implant, or not released until later, the duration of treatment or the rate of release may not be as long as desired. This can cause the implant to be therapeutically less effective.

[0012] In addition, many drug delivery systems may demonstrate a great variation in the rate of drug release over the period of implantation. In these cases, an optimal rate of drug release may be seen only during a very small window over the period of implantation.

SUMMARY OF THE INVENTION

[0013] Generally, the present invention relates to implantable medical articles that include a biodegradable coating. The coating comprises a matrix of hydrophobic derivatives of natural biodegradable polysaccharides (also referred to herein as "hydrophobic polysaccharides").

[0014] In some aspects, the coating includes a bioactive agent, which can be released from the coating after the implantable medical article is placed within a subject. The present invention also relates to treating medical conditions using medical articles having biodegradable coatings formed of the hydrophobic polysaccharides.

[0015] Coating compositions including hydrophobic polysaccharides adhere well to the surface of medical articles to which they are applied, and form coatings with properties that are desirable for use in the body. The biodegradable coatings of the invention are shown herein to demonstrate one more of the following properties, such as compliance, conformability, and/or durability, which provide(s) benefits for in vivo use. These properties can prevent or minimize cracking, delamination, and/or abrasion of the coating when the coated medical article is manipulated during steps in involving placement of the coated article in the body.

[0016] The hydrophobic polysaccharides can be used in combination with various coating solvents, allowing the preparation of compositions that can be suitably mixed with

a variety of excipients or bioactive agents. The coating compositions can also be prepared having a high concentration of solids, allowing the formation of, in some embodiments, a coating having a high content of bioactive agent. The coating materials can also be readily applied to surfaces of implantable medical articles using conventional coating methods, such as spray coating and dip coating.

[0017] The matrix of hydrophobic polysaccharides that form the coating can be degraded into natural materials, which in turn improve the compatibility of the device. Degradation of the coating can result in the release of, for example, naturally occurring mono- or disaccharides, such as glucose, which are common serum components. This provides an advantage over coatings formed from polyglycolide-type molecules, which can degrade into products that cause unwanted side effects in the body by virtue of their presence or concentration in vivo.

[0018] In some aspects, the invention provides an implantable medical article comprising a biodegradable bioactive-agent releasing coating. The coating comprises a matrix of hydrophobic derivatives of natural biodegradable polysaccharides and bioactive-agent within the matrix, and the coating is capable of releasing bioactive agent following placement of the medical article in a subject.

[0019] Preferably, the coatings of the present invention include hydrophobic derivatives of lower molecular weight natural biodegradable polysaccharides, wherein the hydrophobic derivatives have a molecular weight of about 500,000 Da or less. Even more preferably hydrophobic derivatives having a molecular weight of about 100,000 Da or less, 50,000 Da or less, 25,000 Da or less, or in the range of 2000 Da to about 20,000 Da, or in the range of 4000 to 10,000 Da, are used to form the coating.

[0020] In some aspects, the coatings are formed from low molecular weight hydrophobic derivatives of α-1,4 glucopyranose polymers. For example, the implants can be formed from a polymer selected from hydrophobic derivatives of maltodextrin, polyalditol, amylose, and cyclodextrin polymers. In some aspects the hydrophobic derivative is a non-cyclic glucopyranose polymer. In some aspects the hydrophobic derivative is a linear glucopyranose polymer.

[0021] A hydrophobic derivative can include a hydrophobic portion comprising a plurality of groups pendent from a polysaccharide backbone, the groups comprising a hydrocarbon segment. In some aspects, the hydrocarbon segment selected from linear, branched, and cyclic. C_2-C_{18} groups. In more specific aspects, the hydrocarbon segment is selected from, linear, branched, and cyclic C_4-C_8 groups, and even more specific aspects, from linear, branched, or cyclic C_5-C_7 groups.

[0022] The hydrocarbon segment can be saturated or unsaturated, and can include linear, branched, and cyclic alkyl groups, or aromatic groups.

[0023] In many aspects the degree of substitution of the groups on the hydrophobic derivative is about 1 or greater, or in the range of about 2 to 3.

[0024] In many aspects the groups are cleavable from the polysaccharide backbone. For example, the groups that include the hydrocarbon segment are coupled to the polysaccharide backbone of the hydrophobic derivatives via a hydrolyzable ester bond. Following implantation, the groups that include the hydrocarbon segment can be cleaved from the polysaccharide backbone. As a result, the surface of the coating can be come more hydrophilic and result in loss of the coating material by solubilization and/or enzymatic degradation due to the loss of repulsion of fluids.

[0025] In yet other aspects the hydrocarbon segment is a short chain branched alkyl group. It has been found that very compliant and durable hydrophobic coatings can be formed from hydrophobic derivatives having short chain branched alkyl groups pendent from the polysaccharide backbone, at relatively low degrees of substitution. This is advantageous for the preparation of coatings that have a relatively fast rate of degradation. Given the low degree of substitution, loss of the short chain branched alkyl group causes an abrupt change in property of the hydrophobic polysaccharide to hydrophilic, and promotes loss and degradation of portions of the coating at a relatively rapid rate. Exemplary short chain branched alkyl group are branched C_4-C_{10} groups. In many aspects the degree of substitution of the short chain branched alkyl group on the hydrophobic derivative is in the range of 0.5-1.5.

[0026] The coating can be formed using hydrophobic polysaccharides having a desired glass transition temperature (Tg). In some aspects, the coating is formed from hydrophobic derivatives having a Tg of 35° C. or greater, about 40° C. or greater, such as in the range of about 40° C. to about 90° C.

[0027] In some aspects, the coating includes a hydrophilic biocompatible polymer. A hydrophilic biocompatible polymer can increase the rate of release of bioactive agent from the coating. In some aspects, the hydrophilic polymer is selected from the group consisting of poly(ethylene glycol), hydrophilic polysaccharides, polyvinyl pyrrolidones, polyvinyl alcohols, low molecular weight methyl cellulose, hydroxypropyl methyl cellulose (HPMC), and the like. In some aspects, the coating comprises up to about 10% wt of the hydrophilic biocompatible polymer.

[0028] The coatings of the invention can be formed on a surface of any medical device hat is introduced temporarily or permanently into a subject for the prophylaxis or treatment 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 atria of the heart, or in a portion of the eye. The device can be a biostable device, a partially degradable device, or a completely degradable device. For example, stents fabricated from degradable or erodable metalic or polymeric materials can be coated with the hydrophobic polysaccharides of the invention.

[0029] According to the materials and methods described herein, stents having coatings that were formed from hydrophobic polysaccharides were prepared and tested for degradation and bioactive agent release both in vitro and in vivo.

[0030] Results of the experimental studies of the present invention showed that bioactive agent was released from the coating on the stents during the period of implantation in vivo. Ex situ analysis showed loss of the coating formed of the hydrophobic natural biodegradable polysaccharides after the implantation period. It was shown in a porcine model that approximately 50% of the coating comprising the hydrophobic natural biodegradable polysaccharide and a drug was remaining after 28 days of implantation. In view of this, the coatings of the invention can be formed on the surface of an implantable medical article and used for the site-specific treatment of any one of a variety of medical conditions.

[0031] Results also showed the coatings of the invention provided a moderate or minimal initial burst of bioactive agent, and no late stage burst. This is beneficial, as depletion of substantial amounts of bioactive agent from the coating at an early stage following implantation can be avoided.

[0032] The coatings were also prepared having a high bioactive agent load, but were still able to release the bioactive agent at a steady, therapeutically effective rate. This allows the coated implantable articles to be useful for the prolonged release of bioactive agents to treat medical conditions.

[0033] Various types of bioactive agents can be delivered from the coating. Exemplary bioactive agents include, anti-proliferative agents, anti-inflammatory agents, angiogenesis inhibitors, neuroprotective agents, beta adrenergic agents, prostaglandins, or combinations thereof.

[0034] In some aspects, bioactive agent is present in an amount up to about 65 wt % of the implant, such as in the range of about 10 wt % to about 65 wt %, up to about 55% wt, such as in the range of about 25 wt % to about 55 wt %, or about 40 wt % to about 50 wt %.

[0035] In some aspects the bioactive agent is coupled to and cleavable from the polysaccharide backbone. Like the groups that include the hydrocarbon segment, a bioactive agent can be coupled to the polysaccharide backbone via a hydrolyzable ester bond. In some aspect, the bioactive agent can include a hydrocarbon segment, which can contribute the hydrophobic properties of the hydrophobic polysaccharide.

[0036] For example, in some cases the coatings can be formed to release the bioactive agent in a therapeutically useful amount for a period of time greater than one month, three months, six months, a year, and even to about two years. Given the prolonged release of bioactive agent, the need for periodic administration of the bioactive agent is not required. This is beneficial as it eliminates or significantly reduces need for patient compliance.

[0037] In addition, it was found that changes to the biodegradable polysaccharide chemistry and/or coating composition could be made to alter the release rate of the bioactive agent within therapeutically useful ranges. This "tunability" of bioactive release represents an advantage for implantable medical articles, as specific daily doses of bioactive agent can be provided to a subject.

[0038] The invention also provides a method for delivering a bioactive agent to a subject. The method comprises a step of implanting at a target site in a subject an implantable medical article comprising a biodegradable bioactive-agent releasing coating, the coating comprising a matrix of hydrophobic derivatives of natural biodegradable polysaccharides and bioactive agent within the matrix. The method also comprises a step of allowing the bioactive agent to be released from the coating in the subject following the step of implanting.

[0039] The coatings of the invention can release bioactive agent in a therapeutically effective range, such as an amount of nanograms per day, up to about tens of micrograms per day. In some aspects, the bioactive agent is released from the coating in an amount in the range of about 0.01 microgram per day to about 10 micrograms per day.

[0040] In some specific aspects, the method for delivering a bioactive agent to a subject is performed for the treatment of an ocular condition or indication. In the step of implanting, an ocular article having a coating in implanted at a location in the eye. The ocular article is maintained in the eye for a period of time sufficient for the treatment of the ocular condition of indication.

[0041] The invention also provides methods for forming a coating on implantable medical articles. The method comprises a step of preparing a coating composition comprising hydrophobic derivatives of natural biodegradable polysaccharides and bioactive-agent.

[0042] A step of applying the coating composition on a surface of a medical article to form a coating is then performed. Given the properties of the hydrophobic polysaccharide, a coating composition having bioactive at a high concentration can be prepared in a suitable solvent. The composition can then be applied by a technique such as spray coating or dip coating.

[0043] In another aspect of the invention, the coating can be formed on a surface of the device without a bioactive agent. The coating can be used as a degradable barrier that temporarily prevents contact of body fluids or tissues with the structural material of the implantable medical article. In some cases this can improve the biocompatibility of the article by shielding its surface.

[0044] In other cases the coating is formed on the surface of an implantable medical article that is formed from a material that erodes or degrades in the body. The coating of the invention therefore functions to slow the erosion or degradation of the structural portion of the implantable medical article, and lengthen its in vivo lifetime. The coated article can be completely erodable or degradable in vivo, and therefore not require removal after implantation and a period of treatment. In some aspects the coatings of the invention are formed on the surface of an erodable or degradable stent formed of a metal, such as magnesium, or formed of a polymer.

[0045] Therefore, in another aspect, the invention provides an implantable medical article comprising a biodegradable coating. The coating comprises a matrix of hydrophobic derivatives of natural biodegradable polysaccharides, wherein the coating is capable of temporarily shielding the structural portion of the implantable medical article following implantation. In some aspects the implantable medical article is erodable or degradable.

[0046] Therefore, in another aspect, the invention provides an implantable medical article comprising a biodegradable coating. The coating comprises a matrix of hydrophobic derivatives of natural biodegradable polysaccharides, wherein the coating is capable of temporarily shielding the structural portion of the implantable medical article following implantation. In some aspects the implantable medical article is erodable or degradable.

[0047] In another aspect, the invention provides a method for prolonging the in vivo lifetime of an implantable medical article that is formed from an erodable or degradable material. The method comprises a step of forming a coating on the surface of an implantable medical article that is formed from an erodable or degradable material, the coating comprising a matrix of hydrophobic derivatives of natural biodegradable polysaccharides. The method also comprises a step of implanting at a target site in a subject the implantable medical article having the coating. Following implantation, the coated article has an in vivo lifetime that is longer than an in vivo lifetime of an implantable medical article without the coating.

[0048] In another aspect, the invention provides a method for treating a cardiovascular disease or a cardiovascular condition. The method comprises step of implanting at an intravascular site in a subject an implantable prosthesis comprising a biodegradable coating, the coating comprising a matrix of hydrophobic derivatives of natural biodegradable polysaccharides. The method also comprises a step of maintaining the prosthesis at the site for a period of time to treat the cardiovascular disease or a cardiovascular condition. In some aspects the implantable prosthesis is a stent. In some aspects the coating comprises a bioactive agent which is released to the subject during the step of maintaining.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] FIG. **1** is a graph illustrating elution profiles of stents coated with lidocaine and hydrophobic derivatives of natural biodegradable polysaccharides.

DETAILED DESCRIPTION

[0050] The embodiments of the present invention described herein 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.

[0051] All publications and patents mentioned herein are hereby incorporated by reference. The publications and patents disclosed herein are provided solely for their disclosure. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate any publication and/or patent, including any publication and/or patent cited herein.

[0052] The invention is generally directed to coatings formed of a matrix comprising hydrophobic derivatives of natural biodegradable polysaccharides. The coatings can be formed on all or a portion of the surface of an implantable medical article. In some aspects, bioactive agent can be included within the coating, and releasable from the coating following implantation of the article in a patient. In related aspects, the invention is also directed to methods for delivering bioactive agents to a subject from the coatings on the implantable medical articles. The invention is also related to coatings formed of the hydrophobic polysaccharides that are used as a temporary barrier on the surface of implantable medical devices. The invention is also directed to methods for preparing the medical implants of the invention.

[0053] The hydrophobic polysaccharide can be present in one or more coated layers, on all or a portion of the surface of the implantable medical article. A "coating" as used herein can include one or more "coated layers", each coated layer including one or more coating materials. In some cases, the coating can be formed of a single layer of material that includes the hydrophobic polysaccharide. In other cases, the coating includes more than one coated layer, at least one of the coated layers including the hydrophobic polysaccharide. If more than one layer is present in the coating, the layers can be composed of the same or different materials.

[0054] If a bioactive agent is included in the coating it can be in the same coated layer as the hydrophobic polysaccharide, or in a different coated layer. The bioactive agent can be released from the coating upon degradation of the coated layer that includes the hydrophobic polysaccharide. Alternatively, or additionally, the coated layer that includes the hydrophobic polysaccharide can modulate bioactive agent release. In this aspect some or no degradation of the coated layer that includes the hydrophobic polysaccharide may occur.

[0055] The following list of medical articles is provided to illustrate surfaces on which the hydrophobic polysaccharide can be applied to form a coating.

[0056] These types of articles are typically introduced temporarily or permanently into a mammal for the prophylaxis or treatment of a medical condition. For example, these articles can be introduced subcutaneously, percutaneously or surgically to rest within an organ, tissue, or lumen of an organ, such as arteries, veins, ventricles, or atria of the heart.

[0057] Exemplary medical articles include vascular implants and grafts, grafts, surgical devices; synthetic prostheses; vascular prosthesis including endoprosthesis, stent-graft, and endovascular-stent combinations; small diameter grafts, abdominal aortic aneurysm grafts; wound dressings and wound management device; hemostatic barriers; mesh and hernia plugs; patches, including uterine bleeding patches, atrial septic defect (ASD) patches, patent foramen ovale (PFO) patches, ventricular septal defect (VSD) patches, and other generic cardiac patches; ASD, PFO, and VSD closures; percutaneous closure devices, mitral valve repair devices; left atrial appendage filters; valve annuloplasty devices, catheters; central venous access catheters, vascular access catheters, abscess drainage catheters, drug infusion catheters, parenteral feeding catheters, intravenous catheters (e.g., treated with antithrombotic agents), stroke therapy catheters, blood pressure and stent graft catheters; anastomosis devices and anastomotic closures; aneurysm exclusion devices; biosensors including glucose sensors; cardiac sensors; birth control devices; breast implants; infection control devices; membranes; tissue scaffolds; tissue-related materials; shunts including cerebral spinal fluid (CSF) shunts, glaucoma drain shunts; dental devices and dental implants; ear devices such as ear drainage tubes, tympanostomy vent tubes; ophthalmic devices; cuffs and cuff portions of devices including drainage tube cuffs, implanted drug infusion tube cuffs, catheter cuff, sewing cuff; spinal and neurological devices; nerve regeneration conduits; neurological catheters; neuropatches; orthopedic devices such as orthopedic joint implants, bone repair/augmentation devices, cartilage repair devices; urological devices and urethral devices such as urological implants, bladder devices, renal devices and hemodialysis devices, colostomy bag attachment devices; biliary drainage products.

[0058] In some aspects, the biodegradable coating is formed on an ophthalmic article. The ophthalmic article can be configured for placement at an external or internal site of the eye. Suitable ophthalmic devices can also be utilized to provide bioactive agent to tissues in proximity to the eye, when desired.

[0059] Implantable articles configured for placement at an internal site of the eye can reside within any desired area of the eye. In some aspects, the ophthalmic article 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. Pat. No. 6,719,750 B2, which describes a non-linear intraocular device ("Devices for Intraocular Drug Delivery," Varner et al.) and U.S. Pat. No. 5,466,233 ("Tack for Intraocular Drug Delivery and

Method for Inserting and Removing Same," Weiner et al.); U.S. Publication Nos. 2005/0019371 A1 ("Controlled Release Bioactive Agent Delivery Device," Anderson et al.), and 2004/0133155 A1 ("Devices for Intraocular Drug Delivery," Varner et al.) and related applications.

[0060] In some aspects, the biodegradable coating is formed on a stent. Stents include vascular stents such as self-expanding stents and balloon expandable stents. "Expandable" means the stent can be expandable from a reduced diameter configuration utilizing an expansion member, such as a balloon. The particular configuration of the stent body is not critical to the invention described herein, and the inventive biodegradable materials and methods can be applied to virtually any stent configuration.

[0061] It can be desirable to fabricate the stent such that the material is nonsolid. In other words, desirable to include pores or other passages through the material that can enable endothelial cells at the implantation site to grow into and over the stent so that biodegradation will occur within the vessel wall rather than in the lumen of the vessel, which could lead to embolization of the dissolved material.

[0062] In some cases the implantable medical article is partially or entirely fabricated from a plastic polymer. In this regard, the biodegradable coating can be formed on a plastic surface. Plastic polymers 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, vinylidene difluoride, and styrene. 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), polydimethylsiloxanes, and polyetherketone.

[0063] Other suitable polymers for the substrate material include polyamides, polyimides, polyolefins, polystyrenes, polyesters, polycarbonates, polyketones, polyureas, acrylonitrile butadiene copolymers, butadiene rubber, chlorinated and chloro-sulfonated polyethylene, polychloroprene, ethylene propylene (EPM) copolymers, ethylene propylene diene (EPDM) copolymers, polyethylene-ethylene propylene diene PE-EPDM copolymers, polypropylene-ethylene propylene diene (PP-EPDM) copolymers, ethylene-vinyl alcohol copolymer (EVOH), polyepichlorihydrin, isobutylene isoprene copolymer, polyisoprene, polysulfides, silicones polymers, nitrile butadiene copolymer/polyvinylchloride blends (NBR/PVC), styrene butadiene copolymers, and vinyl acetate ethylene copolymers, and combinations thereof.

[0064] In some cases the implantable medical article is partially or entirely fabricated from a degradable polymer. The article can degrade in an aqueous environment, such as by simple hydrolysis, or can be enzymatically degraded.

[0065] Examples of classes of synthetic polymers that can be used to form the structure of the article include polyesters, polyamides, polyurethanes, polyorthoesters, polycaprolactone (PCL), polyiminocarbonates, aliphatic carbonates, polyphosphazenes, polyanhydrides, and copolymers thereof. Specific examples of biodegradable materials that can be used in connection with the device of the invention include polylactide, polygylcolide, polydioxanone, poly(lactide-co-glycolide), poly(glycolide-co-polydioxanone), polyanhydrides, poly(glycolide-co-trimethylene carbonate), and poly (glycolide-co-caprolactone). As an example, the hydrophobic polysaccharide can provide a barrier coating to articles fabricated from PLA or copolymers thereof. The coating can shield the article during a portion or all of a desired period of treatment. The coating article can still be fully degradable.

[0066] Blends of these polymers with other biodegradable polymers can also be used.

[0067] In other cases, the coating can be formed on a medical device that is partially or entirely fabricated from a metal. Although many devices or articles are constructed from substantially all metal materials, such as alloys, some may be constructed from both non-metal and metal materials, where at least a portion of the surface of the device is metal. The metal surface may also be a thin surface layer. Such surfaces can be formed by any method including sputter coating metal onto all or portions of the surface of the device.

[0068] Metals that can be used in medical articles include platinum, gold, or tungsten, as well as other metals such as rhenium, palladium, rhodium, ruthenium, titanium, nickel, and alloys of these metals, such as stainless steel, titanium/nickel, nitinol alloys, cobalt chrome alloys, non-ferrous alloys, and platinum/iridium alloys. One exemplary alloy is MP35. These metals, including other alloys or combinations, can be suitable substrates for disposing a coating composition containing the hydrophobic polysaccharides of the invention.

[0069] The surface of metal-containing medical devices can be pretreated (for example, with a Parylene™-containing coating composition) in order to alter the surface properties of the biomaterial, when desired. Metal surfaces can also be treated with silane reagents, such as hydroxy- or chloro-silanes.

[0070] In some aspects the biodegradable coating is formed on the surface of an erodable implantable medical device formed from of a metal. For example, the biodegradable coating can be formed on a magnesium alloy stent that can be corroded following placement in a subject (see, for example, De Mario, C. et al. (2004) *J. Interv. Cardiol.,* 17(6):391-395, and Heublein, B., et al. (2003) *Heart;* 89:651-656). The erodable implantable medical device can also include a bioactive agent, if desired.

[0071] In aspects where the structure of the implantable medical article is fabricated from a material that is erodable or degradable, an in vivo lifetime of the article can be determined. The biodegradable coatings of the present invention can be applied to the surface of these erodable or degradable articles to prolong their in vivo lifetime. The in vivo lifetime is a period of time starting upon placement of the coated article at a target location, and ending when the coated article is completely degraded at the target location.

[0072] Other surfaces that can be optionally coated include those that include human tissue such as bone, cartilage, skin and teeth; or other organic materials such as wood, cellulose, compressed carbon, and rubber. Other contemplated biomaterials include ceramics including, but not limited to, silicon nitride, silicon carbide, zirconia, and

alumina, as well as glass, silica, and sapphire. Combinations of ceramics and metals can also be coated.

[0073] In some aspects, a bioactive agent can be released from the coated article during the entire in vivo lifetime, or during a portion of the coated article's in vivo lifetime. The bioactive agent can be present in the coating, within the structure of the article itself, or in both.

[0074] The period of time in which the bioactive agent is released from the coated article is referred to as the "bioactive agent release period." If the bioactive agent release period is less than the in vivo lifetime of the coating, the bioactive agent is generally released from the coating at a rate faster than loss and/or degradation of the hydrophobic polysaccharide from the coating. In this case, release of the bioactive agent out of the coating, such as by diffusion, may cause the bioactive agent release period to be less than the in vivo lifetime of the coating.

[0075] A "subject" refers to an organism in which the coated medical article is placed and which the bioactive agent becomes available in following implantation. The subject can be a patient having a medical condition, wherein the condition is treatable using a bioactive agent that is released from the medical implants of the invention. The subject can be a human, another mammal, or a non-mammalian organism. For example, the subject can be a domesticated mammal such as a dog, cat, horse, cow, sheep, rabbit, etc. The subject can also be a bird, fish, or reptile.

[0076] The coating includes a matrix of hydrophobic derivatives of natural biodegradable polysaccharides. The matrix is formed via hydrophobic interactions of the hydrophobic portion of the polysaccharide. Bioactive agent, if included in the coating, can be held within the matrix. The bioactive agent is released to the subject after the coated article is delivered to a target location in the body.

[0077] As used herein, a "hydrophobic derivative" of a natural biodegradable polysaccharide refers to a natural biodegradable polysaccharide having one or more pendent groups attached to the polysaccharide. In many cases the hydrophobic derivative includes a plurality of groups comprising hydrocarbon segments attached to the polysaccharide. When a plurality of groups comprising hydrocarbon segments is attached they are collectively referred to as the "hydrophobic portion" of the hydrophobic derivative. The hydrophobic derivatives of the invention therefore include a hydrophobic portion and a polysaccharide portion.

[0078] The coating of the present invention is described as being formed from a "matrix" of hydrophobic derivative of a natural biodegradable polysaccharide. Generally, the matrix provides the structural framework of the coating, which is established by association of the groups comprising the hydrocarbon segments that are pendent from the polysaccharide backbone. The structural integrity of the coating can therefore be in part based on the hydrophobic interactions in the matrix. Optionally, the matrix can optionally include other types of non-hydrophobic associations between polysaccharides, such as covalent or non-covalent crosslinks which may be formed by groups pendent from the polysaccharide or groups independent of the polysaccharide.

[0079] The polysaccharide portion comprises a "natural biodegradable polysaccharide," which refers to a non-synthetic polysaccharide that is capable of being enzymatically degraded. Natural biodegradable polysaccharides include polysaccharide and/or polysaccharide derivatives that are obtained from natural sources, such as plants or animals. Natural biodegradable polysaccharides include any polysaccharide that has been processed or modified from a natural biodegradable polysaccharide (for example, maltodextrin is a natural biodegradable polysaccharide that is processed from starch). Exemplary natural biodegradable polysaccharides include maltodextrin, amylose, cyclodextrin, polyalditol, hyaluronic acid, dextran, heparin, chondroitin sulfate, dermatan sulfate, heparan sulfate, keratan sulfate, dextran, dextran sulfate, pentosan polysulfate, and chitosan. Preferred polysaccharides are low molecular weight polymers that have little or no branching, such as those that are derived from and/or found in starch preparations, for example, maltodextrin, amylose, and cyclodextrin. Therefore, the natural biodegradable polysaccharide can be a substantially non-branched or completely non-branched poly(glucopyranose) polymer.

[0080] As used herein, "amylose" or "amylose polymer" refers to a linear polymer having repeating glucopyranose units that are joined by α-1,4 linkages. Some amylose polymers can have a very small amount of branching via α-1,6 linkages (about less than 0.5% of the linkages) but still demonstrate the same physical properties as linear (unbranched) amylose polymers do. Generally amylose polymers derived from plant sources have molecular weights of about 1×10^6 Da or less. Amylopectin, comparatively, is a branched polymer having repeating glucopyranose units that are joined by α-1,4 linkages to form linear portions and the linear portions are linked together via α-1,6 linkages. The branch point linkages are generally greater than 1% of the total linkages and typically 4%-5% of the total linkages. Generally amylopectin derived from plant sources have molecular weights of 1×10^7 Da or greater.

[0081] Amylose can be obtained from, or is present in, a variety of sources. Typically, amylose is obtained from non-animal sources, such as plant sources. In some aspects, a purified preparation of amylose is used as starting material for the preparation of the amylose polymer having pendent groups comprising pendent groups that include hydrocarbon segments. In other aspects, as starting material, amylose can be used in a mixture that includes other polysaccharides.

[0082] For example, in some aspects, starch preparations having a high amylose content, purified amylose, synthetically prepared amylose, or enriched amylose preparations can be used in the preparation of a hydrophobic derivative of amylose. In starch sources, amylose is typically present along with amylopectin, which is a branched polysaccharide. If a mixture of amylose and a higher molecular weight precursor is used (such as amylopectin), it is preferred that amylose is present in the composition in an amount greater than the higher molecular weight precursor. For example, in some aspects, starch preparations having high amylose content, purified amylose, synthetically prepared amylose, or enriched amylose preparations can be used in the preparation of a hydrophobic derivative of amylose polymer. In some embodiments the composition includes a mixture of polysaccharides including amylose wherein the amylose content in the mixture of polysaccharides is 50% or greater, 60% or greater, 70% or greater, 80% or greater, or 85% or greater by weight. In other embodiments the composition includes a mixture of polysaccharides including amylose and amylopectin and wherein the amylopectin content in the mixture of polysaccharides is 30% or less, or 15% or less.

[0083] The amount of amylopectin present in a starch may also be reduced by treating the starch with amylopectinase, which cleaves α-1,6 linkages resulting in the debranching of amylopectin into amylose.

[0084] Steps may be performed before, during, and/or after the process of derivatizing the amylose polymer with a pendent group comprising a hydrocarbon segment to enrich the amount of amylose, or purify the amylose.

[0085] Amylose of particular molecular weights can be obtained commercially or can be prepared. For example, synthetic amyloses with average molecular masses of 70 kDa, 110 kDa, and 320 kDa, can be obtained from Nakano Vinegar Co., Ltd. (Aichi, Japan). The decision of using amylose of a particular size range may depend on factors such as the physical characteristics of the composition (e.g., viscosity), the desired rate of degradation of the coating formed from the hydrophobic derivative, and the presence of other optional components in the composition, such as bioactive agents.

[0086] Purified or enriched amylose preparations can be obtained commercially or can be prepared using standard biochemical techniques such as chromatography. In some aspects, high-amylose cornstarch can be used to prepare the hydrophobic derivative.

[0087] Maltodextrin is typically generated by hydrolyzing a starch slurry with heat-stable a-amylase at temperatures at 85-90° C. until the desired degree of hydrolysis is reached and then inactivating the α-amylase by a second heat treatment. The maltodextrin can be purified by filtration and then spray dried to a final product. Maltodextrins are typically characterized by their dextrose equivalent (DE) value, which is related to the degree of hydrolysis defined as: DE=MW dextrose/number-averaged MW starch hydrolysate X 100. Generally, maltodextrins are considered to have molecular weights that are less than amylose molecules.

[0088] A starch preparation that has been totally hydrolyzed to dextrose (glucose) has a DE of 100, whereas starch has a DE of about zero. A DE of greater than 0 but less than 100 characterizes the mean-average molecular weight of a starch hydrolysate, and maltodextrins are considered to have a DE of less than 20. Maltodextrins of various molecular weights, for example, in the range of about 500 Da to 5000 Da are commercially available (for example, from CarboMer, San Diego, Calif.).

[0089] Another contemplated class of natural biodegradable polysaccharides is natural biodegradable non-reducing polysaccharides. A non-reducing polysaccharide can provide an inert matrix thereby improving the stability of sensitive bioactive agents, such as proteins and enzymes. A non-reducing polysaccharide refers to a polymer of non-reducing disaccharides (two monosaccharides linked through their anomeric centers) such as trehalose (α-D-glucopyranosyl α-D-glucopyranoside) and sucrose (β-D-fructofuranosyl α-D-glucopyranoside). An exemplary non-reducing polysaccharide comprises polyalditol which is available from GPC (Muscatine, Iowa). In another aspect, the polysaccharide is a glucopyranosyl polymer, such as a polymer that includes repeating (1→3)O-β-D-glucopyranosyl units.

[0090] Dextran is an α-D-1,6-glucose-linked glucan with side-chains 1-3 linked to the backbone units of the dextran biopolymer. Dextran includes hydroxyl groups at the 2, 3, and 4 postions on the glucopyranose monomeric units. Dextran can be obtained from fermentation of sucrose-containing media by *Leuconostoc mesenteroides* B512F.

[0091] Dextran can be obtained in low molecular weight preparations. Enzymes (dextranases) from molds such as *Penicillium* and *Verticillium* have been shown to degrade dextran. Similarly many bacteria produce extracellular dextranases that split dextran into low molecular weight sugars.

[0092] Chondroitin sulfate includes the repeating disaccharide units of D-galactosamine and D-glucuronic acid, and typically contains between 15 to 150 of these repeating units. Chondroitinase AC cleaves chondroitin sulfates A and C, and chondroitin.

[0093] Hyaluronic acid (HA) is a naturally derived linear polymer that includes alternating β1,4-glucuronic acid and β1,3-N-acetyl-D-glucosamine units. HA is the principal glycosaminoglycan in connective tissue fluids. HA can be fragmented in the presence of hyaluronidase.

[0094] In many aspects the polysaccharide portion and the hydrophobic portion comprise the predominant portion of the hydrophobic derivative of the natural biodegradable polysaccharide. Based on a weight percentage, the polysaccharide portion can be about 25% wt of the hydrophobic derivative or greater, in the range of about 25% to about 75%, in the range of about 30% to about 70%, in the range of about 35% to about 65%, in the range of about 40% to about 60%, or in the range of about 45% to about 55%. Likewise, based on a weight percentage of the overall hydrophobic derivative, the hydrophobic portion can be about 25% wt of the hydrophobic derivative or greater, in the range of about 25% to about 75%, in the range of about 30% to about 70%, in the range of about 35% to about 65%, in the range of about 40% to about 60%, or in the range of about 45% to about 55%. In exemplary aspects, the hydrophobic derivative has approximately 50% of its weight attributable to the polysaccharide portion, and approximately 50% of its weight attributable to its hydrophobic portion.

[0095] The hydrophobic derivative has the properties of being insoluble in water. The term for insolubility is a standard term used in the art, and meaning 1 part solute per 10,000 parts or greater solvent. (see, for example, Remington: The Science and Practice of Pharmacy, 20th ed. (2000), Lippincott Williams & Wilkins, Baltimore Md.).

[0096] A hydrophobic derivative can be prepared by associating one or more hydrophobic compound(s) with a natural biodegradable polysaccharide polymer. Methods for preparing hydrophobic derivatives of natural biodegradable polysaccharides are described herein.

[0097] The hydrophobic derivatives of the natural biodegradable polysaccharides preferably have a molecular weight of 500,000 Da or less. Use of these lower molecular weight derivatives provides implants with desirable physical and drug-releasing properties. In some aspects the hydrophobic derivatives have a molecular weight of about 250,000 Da or less, about 100,000 Da or less, about 50,000 Da or less, or 25,000 Da or less. Particularly preferred size ranges for the natural biodegradable polysaccharides are in the range of about 2,000 Da to about 20,000 Da, or about 4,000 Da to about 10,000 Da.

[0098] The molecular weight of the polymer is more precisely defined as "weight average molecular weight" or M_w. M_w is an absolute method of measuring molecular weight and is particularly useful for measuring the molecular weight of a polymer (preparation). Polymer preparations

typically include polymers that individually have minor variations in molecular weight. Polymers are molecules that have a relatively high molecular weight and such minor variations within the polymer preparation do not affect the overall properties of the polymer preparation. The weight average molecular weight (M_w) can be defined by the following formula:

$$M_w = \frac{\sum_i N_i M_i^2}{\sum_i N_i M_i}$$

wherein N represents the number of moles of a polymer in the sample with a mass of M, and Σ_s is the sum of all N_iM_i (species) in a preparation. The M_w can be measured using common techniques, such as light scattering or ultracentrifilgation. Discussion of M_w and other terms used to define the molecular weight of polymer preparations can be found in, for example, Allcock, H. R. and Lampe, F. W. (1990) *Contemporary Polymer Chemistry;* pg 271.

[0099] The addition of hydrophobic portion will generally cause an increase in molecular weight of the polysaccharide from its underivitized, starting molecular weight. The amount increase in molecular weight can depend on one or more factors, including the type of polysaccharide derivatized, the level of derivation, and, for example, the type or types of groups attached to the polysaccharide to provide the hydrophobic portion.

[0100] In some aspects, the addition of hydrophobic portion causes an increase in molecular weight of the polysaccharide of about 20% or greater, about 50% or greater, about 75% or greater, about 100% or greater, or about 125%, the increase in relation to the underivitized form of the polysaccharide.

[0101] As an example, a maltodextrin having a starting weight of about 3000 Da is derivitized to provide pendent hexanoate groups that are coupled to the polysaccharide via ester linkages to provide a degree of substitution (DS) of about 2.5. This provides a hydrophobic polysaccharide having a theoretical molecular weight of about 6000 Da.

[0102] In forming the hydrophobic derivative of the natural biodegradable polysaccharide and as an example, a compound having a hydrocarbon segment can be covalently coupled to one or more portions of the polysaccharide. For example, the compound can be coupled to monomeric units along the length of the polysaccharide. This provides a polysaccharide derivative with one or more pendent groups. Each chemical group comprises a hydrocarbon segment. The hydrocarbon segment can constitute all of the pendent chemical group, or the hydrocarbon segment can constitute a portion of the pendent chemical group. For example, a portion of the hydrophobic polysaccharide can have the following structure, wherein M is a monomeric unit of the polysaccharide, and in the pendent chemical group ([L]-[H]), H is the hydrocarbon segment, and L is a chemical group linking the hydrocarbon segment to the monomeric unit of the polysaccharide:

[M]-[L]-[H]

[0103] The pendent group can also include an additional portion that is not a hydrocarbon segment [N] as represented by the following structure:

[M]-[L]-[H]—[N]

[0104] A "hydrocarbon segment" herein refers to a group of covalently bonded carbon atoms having the formula $(CH_n)_m$, wherein m is 2 or greater, and n is independently 2 or 1. A hydrocarbon segment can include saturated hydrocarbon groups or unsaturated hydrocarbon groups, and examples thereof include alkyl, alkenyl, alkynyl, cyclic alkyl, cyclic alkenyl, aromatic hydrocarbon and aralkyl groups.

[0105] The monomeric units of the hydrophobic polysaccharides described herein typically include monomeric units having ring structures with one or more reactive groups. These reactive groups are exemplified by hydroxyl groups, such as the ones that are present on glucopyranose-based monomeric units of amylose and maltodextrin. These hydroxyl groups can be reacted with a compound that includes a hydrocarbon segment and a group that is reactive with the hydroxyl group (a hydroxyl-reactive group).

[0106] Examples of hydroxyl reactive groups include acetal, carboxyl, anhydride, acid halide, and the like. These groups can be used to form a hydrolytically cleavable covalent bond between the hydrocarbon segment and the polysaccharide backbone. For example, the method can provide a pendent group having a hydrocarbon segment, the pendent group linked to the polysaccharide backbone with a cleavable ester bond. In these aspects, the synthesized hydrophobic derivative of the natural biodegradable polysaccharide will include chemical linkages that are both enzymatically cleavable (the polymer backbone) and non-enzymatically hydrolytically cleavable (the linkage between the pendent group and the polymer backbone).

[0107] Other cleavable chemical linkages that can be used to bond the pendent groups to the polysaccharide include peroxyester groups, disulfide groups, and hydrazone groups.

[0108] In some cases the hydroxyl reactive groups include those such as isocyanate and epoxy. These groups can be used to form a non-cleavable covalent bond between the pendent group and the polysaccharide backbone. In these aspects, the synthesized hydrophobic derivative of the natural biodegradable polysaccharide includes chemical linkages that are enzymatically cleavable (the polymer backbone).

[0109] Other reactive groups, such as carboxyl groups, acetyl groups, or sulphate groups, are present on the ring structure of monomeric units of other natural biodegradable polysaccharides, such as chondrotin or hyaluronic acid. These groups can also be targeted for reaction with a compound having a hydrocarbon segment to be bonded to the polysaccharide backbone.

[0110] Various factors can be taken into consideration in the synthesis of the hydrophobic derivative of the natural biodegradable polysaccharide. These factors include the physical and chemical properties of the natural biodegradable polysaccharide, including its size, and the number and presence of reactive groups on the polysaccharide and solubility, the physical and chemical properties of the compound that includes the hydrocarbon segment, including its the size and solubility, and the reactivity of the compound with the polysaccharide.

[0111] In preparing the hydrophobic derivative of the natural biodegradable polysaccharide any suitable synthesis procedure can be performed. Synthesis can be carried out to provide a desired number of groups with hydrocarbon segments pendent from the polysaccharide backbone. The number and/or density of the pendent groups can be controlled, for example, by controlling the relative concentra-

tion of the compound that includes the hydrocarbon segment to the available reactive groups (e.g., hydroxyl groups) on the polysaccharide.

[0112] The type and amount of groups having the hydrocarbon segment pendent from the polysaccharide is sufficient for the hydrophobic polysaccharide to be insoluble in water. In order to achieve this, as a general approach, a hydrophobic polysaccharide is obtained or prepared wherein the groups having the hydrocarbon segment pendent from the polysaccharide backbone in an amount in the range of 0.25 (pendent group): 1 (polysaccharide monomer) by weight.

[0113] To exemplify these levels of derivation, very low molecular weight (less than 10,000 Da) glucopyranose polymers are reacted with compounds having the hydrocarbon segment to provide low molecular weight hydrophobic glucopyranose polymers. In one mode of practice, the natural biodegradable polysaccharide maltodextrin in an amount of 10 g (MW 3000-5000 Da; ~3 mmols) is dissolved in a suitable solvent, such as tetrahydrofuran. Next, a solution having butyric anhydride in an amount of 18 g (0.11 mols) is added to the maltodextrin solution. The reaction is allowed to proceed, effectively forming pendent butyrate groups on the pyranose rings of the maltodextrin polymer. This level of derivation results in a degree of substitution (DS) of butyrate group of the hydroxyl groups on the maltodextrin of about 1.

[0114] For maltodextrin and other polysaccharides that include three hydroxyl groups per monomeric unit, on average, one of the three hydroxyl groups per glycopyranose monomeric unit becomes substituted with a butyrate group. A maltodextrin polymer having this level of substitution is referred to herein as maltodextrin-butyrate DS **1**. As described herein, the DS refers to the average number of reactive groups (including hydroxyl and other reactive groups) per monomeric unit that are substituted with pendent groups comprising hydrocarbon segments.

[0115] An increase in the DS can be achieved by incrementally increasing the amount of compound that provides the hydrocarbon segment to the polysaccharide. As another example, butyrylated maltodextrin having a DS of 2.5 is prepared by reacting 10 g of maltodextrin (MW 3000-5000 Da; ~3 mmols) with 0.32 mols butyric anhydride.

[0116] In some modes of practice, the invention provides an coating comprising hydrophobic glucopyranose polymer comprising a DS in the range of about 2-3, comprising pendent linear, branched, or cyclic a C_4-C_{10} groups, and the polymer has a MW in the range of about 2000 to about 20000 Da.

[0117] In some modes of practice, the invention provides an coating comprising hydrophobic glucopyranose polymer comprising a DS in the range of about 2-3, comprising pendent linear, branched, or cyclic C_5-C_7 groups, and the polymer has a MW in the range of about 2000 to about 20000 Da.

[0118] The degree of substitution can influence the hydrophobic character of the polysaccharide. In turn, coatings formed from hydrophobic derivatives having a substantial amount of groups having the hydrocarbon segments bonded to the polysaccharide backbone (as exemplified by a high DS) are generally more hydrophobic and can be more resistant to degradation. For example, a matrix formed from maltodextrin-butyrate DS1 has a rate of degradation that is faster than a matrix formed from maltodextrin-butyrate DS2.

[0119] The type of hydrocarbon segment present in the groups pendent from the polysaccharide backbone can also influence the hydrophobic properties of the polymer. In one aspect, the coating is formed using a hydrophobic polysaccharide having pendent groups with hydrocarbon segments being short chain branched alkyl group. Exemplary short chain branched alkyl group are branched C_4-C_{10} groups. The preparation of a hydrophobic polymer with these types of pendent groups is exemplified by the reaction o maltodextrin with valproic acid/anhydride with maltodextrin (MD-val). The reaction can be carried out to provide a relatively lower degree of substitution of the hydroxyl groups, such as is in the range of 0.5-1.5. Although these polysaccharides have a lower degree of substitution, the short chain branched alkyl group imparts considerable hydrophobic properties to the polysaccharide.

[0120] Even at these low degrees of substitution the MD-val forms coatings that are very compliant and durable. Because of the low degrees of substitution, the pendent groups with the branched C_8 segment can be hydrolyzed from the polysaccharide backbone at a relatively fast rate, thereby providing a biodegradable coatings that have a relatively fast rate of degradation.

[0121] For polysaccharides having hydrolytically cleavable pendent groups comprising hydrocarbon segments, penetration by an aqueous solution can promote hydrolysis and loss of groups pendent from the polysaccharide backbone. This can alter the properties of the implant, and can result in greater access to enzymes that promote the degradation of the natural biodegradable polysaccharide, and/or can result in the loss of the polysaccharides from the coating as they become solubilized.

[0122] Various synthetic schemes can be used for the preparation of a hydrophobic derivative of a natural biodegradable polysaccharide. In some modes of preparation, pendent polysaccharide hydroxyl groups are reacted with a compound that includes a hydrocarbon segment and a group that is reactive with the hydroxyl groups. This reaction can provide polysaccharide with pendent groups comprising hydrocarbon segments.

[0123] Any suitable chemical group can be coupled to the polysaccharide backbone and provide the polysaccharide with hydrophobic properties, wherein the polysaccharide becomes insoluble in water. Preferably, the pendent group includes one or more atoms selected from C, H, O, N, and S.

[0124] In some aspects, the pendent group comprises a hydrocarbon segment that is a linear, branched, or cyclic C_2-C_{18} group. More preferably the hydrocarbon segment comprises a C_2-C_{10}, or a C_4-C_8, linear, branched, or cyclic group. The hydrocarbon segment can be saturated or unsaturated, and can comprise alkyl groups or aromatic groups, respectively. The hydrocarbon segment can be linked to the polysaccharide chain via a hydrolyzable bond or a non-hydrolyzable bond.

[0125] In some aspects the compound having a hydrocarbon segment that is reacted with the polysaccharide backbone is derived from a natural compound. Natural compounds with hydrocarbon segments include fatty acids, fats, oils, waxes, phospholipids, prostaglandins, thromboxanes, leukotrienes, terpenes, steroids, and lipid soluble vitamins.

[0126] Exemplary natural compounds with hydrocarbon segments include fatty acids and derivatives thereof, such as fatty acid anhydrides and fatty acid halides. Exemplary fatty

acids and anhydrides include acetic, propionic, butyric, isobutyric, valeric, caproic, caprylic, capric, and lauric acids and anhydrides, respectively. The hydroxyl group of a polysaccharide can be reacted with a fatty acid or anhydride to bond the hydrocarbon segment of the compound to the polysaccharide via an ester group.

[0127] The hydroxyl group of a polysaccharide can also cause the ring opening of lactones to provide pendent open-chain hydroxy esters. Exemplary lactones that can be reacted with the polysaccharide include caprolactone and glycolides.

[0128] Generally, if compounds having large hydrocarbon segments are used for the synthesis of the hydrophobic derivative, a smaller amount of the compound may be needed for its synthesis. For example, as a general rule, if a compound having a hydrocarbon segments with an alkyl chain length of C_x is used to prepare a hydrophobic derivative with a DS of 1, a compound having a hydrocarbon segment with an alkyl chain length of $C_{(x\times 2)}$ is reacted in an amount to provide a hydrophobic derivative with a DS of 0.5.

[0129] The hydrophobic derivative of the natural biodegradable polysaccharide can also be synthesized having combinations of pendent groups with two or more different hydrocarbon segments, respectively. For example, the hydrophobic derivative can be synthesized using compounds having hydrocarbon segments with different alkyl chain lengths. In one mode of practice, a polysaccharide is reacted with a mixture of two or more fatty acids (or derivatives thereof) selected from the group of acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, caproic acid, caprylic acid, capric acid, and lauric acid to generate the hydrophobic derivative.

[0130] In other cases the hydrophobic derivative is synthesized having a non-hydrolyzable bond linking the hydrocarbon segment to the polysaccharide backbone. Exemplary non-hydrolyzable bonds include urethane bonds.

[0131] The hydrophobic derivative of the natural biodegradable polysaccharide can also be synthesized so that hydrocarbon segments are individually linked to the polysaccharide backbone via both hydrolyzable and non-hydrolyzable bonds. As another example, a hydrophobic derivative is prepared by reacting a mixture of butyric acid anhydride and butyl isocyanate with maltodextrin. This yields a hydrophobic derivative of maltodextrin with pendent butyric acid groups that are individually covalently bonded to the maltodextrin backbone with hydrolyzable ester linkages and non-hydrolyzable urethane linkages. The degradation of a coating having this type of hydrophobic derivative can occur by loss of the butyrate groups from hydrolysis of the ester linkages. However, a portion of the butyrate groups (the ones that are bonded via the urethane groups) are not removed from the polysaccharide backbone and therefore the natural biodegradable polysaccharide can maintain a desired degree of hydrophobicity, prior to enzymatic degradation of the polysaccharide backbone.

[0132] In some aspects, the group that is pendent from the polysaccharide backbone has properties of a bioactive agent. In this regard, the coating comprises polysaccharide-coupled bioactive agent. In some aspects, a bioactive agent which has a hydrocarbon segment can be hydrolyzed from the natural biodegradable polymer and released from the matrix to provide a therapeutic effect. One example of a therapeutically useful compound having a hydrocarbon segments is butyric acid, which has been shown to elicit tumor cell differentiation and apoptosis, and is thought to be useful for the treatment of cancer and other blood diseases.

[0133] Other illustrative compounds comprising hydrocarbon segments include valproic acid and retinoic acid. These compounds can be coupled to a polysaccharide backbone to provide a pendent group, and then cleaved from the polysaccharide backbone following implantation of the coated article in a subject. Retinoic acid is known to possess antiproliferative effects and is thought to be useful for treatment of proliferative vitreoretinopathy (PVR). The pendent group that provides a therapeutic effect can also be a natural compound (such as butyric acid, valproic acid, and retinoic acid).

[0134] Other illustrative compound that can be coupled to the polysaccharide backbone is a corticosteroid. An exemplary corticosteroid is triamcinolone. One method of coupling triamcinolone to a natural biodegradable polymer is by employing a modification of the method described in Cayanis, E. et al., *Generation of an Auto-anti-idiotypic Antibody that Binds to Glucocorticoid Receptor,* The Journal of Biol. Chem., 261(11): 5094-5103 (1986). Triamcinolone hexanoic acid is prepared by reaction of triamcinolone with ketohexanoic acid; an acid chloride of the resulting triamcinolone hexanoic acid can be formed and then reacted with the natural biodegradable polymer, such as maltodextrin or polyalditol, resulting in pendent triamcinolone groups coupled via ester bonds to the natural biodegradable polymer.

[0135] The hydrophobic derivative of the natural biodegradable polysaccharide can also be synthesized having two or more different pendent groups, wherein at least one of the pendent groups comprises a bioactive agent. The hydrophobic polysaccharide can be synthesized with an amount of a pendent groups comprising a bioactive agent, that when released from the polysaccharide, provides a therapeutic effect to the subject. An example of such a hydrophobic derivative is maltodextrin-caproate-triamcinolone. This hydrophobic derivative can be prepared by reacting a mixture including triamcinolone hexanoic acid and an excess of caproic anhydride (n-hexanoic anhydride) with maltodextrin to provide a derivative with a DS of 2.5.

[0136] In some aspects, the group that is pendent from the polysaccharide includes a hydrocarbon segment that is an aromatic group, such as a phenyl group. As one example, o-acetylsalicylic acid is reacted with a polysaccharide such as maltodextrin to provide pendent chemical group having a hydrocarbon segment that is a phenyl group, and a non-hydrocarbon segment that is an acetate group wherein the pendent group is linked to the polysaccharide via an ester bond.

[0137] The term "bioactive agent," refers to an inorganic or organic molecule, which can be synthetic or natural, that causes a biological effect when administered in vivo to a subject. The invention contemplates coatings having bioactive agent within the matrix, but not coupled to the hydrophobic polysaccharide, bioactive agent coupled to the hydrophobic polysaccharide, and combinations thereof. The invention also contemplates coated medical articles wherein the bioactive agent is present in the article (such as within the body member of a biodegradable stent).

[0138] A partial list of bioactive agents is provided below. According to embodiments of the present invention, one may choose one or more of the bioactive agents to be

included in a coating formed of the hydrophobic derivative of the natural biodegradable polysaccharide and/or coated medical article. A comprehensive listing of bioactive agents, in addition to information of the water solubility of the bioactive agents, can be found in *The Merck Index* Thirteenth Edition, Merck & Co. (2001).

[0139] Coatings and/or coated medical articles prepared according to the invention can be used to release bioactive agents falling within one or more of the following classes include, but are not limited to: ACE inhibitors, actin inhibitors, analgesics, anesthetics, anti-hypertensives, anti polymerases, antisecretory agents, anti-AIDS substances, antibiotics, anti-cancer substances, anti-cholinergics, anticoagulants, anti-convulsants, anti-depressants, anti-emetics, antifungals, anti-glaucoma solutes, antihistamines, antihypertensive agents, anti-inflammatory agents (such as NSAIDs), anti metabolites, antimitotics, antioxidizing agents, anti-parasite and/or anti-Parkinson substances, antiproliferatives (including antiangiogenesis agents), anti-protozoal solutes, anti-psychotic substances, anti-pyretics, antiseptics, anti-spasmodics, antiviral agents, calcium channel blockers, cell response modifiers, chelators, chemotherapeutic agents, dopamine agonists, extracellular matrix components, fibrinolytic agents, free radical scavengers, growth hormone antagonists, hypnotics, immunosuppressive agents, immunotoxins, inhibitors of surface glycoprotein receptors, microtubule inhibitors, miotics, muscle contractants, muscle relaxants, neurotoxins, neurotransmitters, polynucleotides and derivatives thereof, opioids, photodynamic therapy agents, prostaglandins, remodeling inhibitors, statins, steroids, thrombolytic agents, tranquilizers, vasodilators, and vasospasm inhibitors.

[0140] Antibiotics are art recognized and are substances that inhibit the growth of or kill microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vancomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromycin, cephalosporins, geldanamycin, and analogs thereof. Examples of cephalosporins include cephalothin, cephapirin, cefazolin, cephalexin, cephradine, cefadroxil, cefamandole, cefoxitin, cefaclor, cefuroxime, cefonicid, ceforanide, cefotaxime, moxalactam, ceftizoxime, ceftriaxone, and cefoperazone.

[0141] Antiseptics are recognized as substances that prevent or arrest the growth or action of microorganisms, generally in a nonspecific fashion, e.g., 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.

[0142] Anti-viral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include α-methyl-P-adamantane methylamine, hydroxy-ethoxymethylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

[0143] 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-hydroxymaleate, iodotubercidin, p-bromotetramisole, 10-(α-diethylaminopropionyl)-phenothiazine hydrochloride, calmidazolium chloride, hemicholinium-3,3,5-dinitrocatechol, diacylglycerol kinase 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-diphenylvalerate 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 L(−), cetazolamide, dichlorphenamide, 6-hydroxy-2-benzothiazolesulfonamide, and allopurinol.

[0144] 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, 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.

[0145] Examples of statins include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and superstatin.

[0146] Examples of steroids include glucocorticoids such as cortisone, hydrocortisone, dexamethasone, betamethasone, prednisone, prednisolone, methylprednisolone, triamcinolone, beclomethasone, fludrocortisone, and aldosterone; sex steroids such as testostersone, dihydrotestosterone, estradiol, diethylstilbestrol, progesterone, and progestins.

[0147] The bioactive agent can be an immunosuppressive agent, for example, rapamycin, ABT-578, cyclosporine, everolimus, mycophenolic acid, sirolimus, tacrolimus, and the like.

[0148] In some cases a coating composition, such as one for a spray coating process, can be prepared having the hydrophobic polysaccharide at a concentration in the range of about 5 mg/mL to about 500 mg/mL in the composition. In one modes of practice the hydrophobic polysaccharide is present in the composition at about 50 mg/mL and the composition is used for coating a surface.

[0149] The coatings of the present invention can be formed by first preparing a coating composition that includes the hydrophobic derivative of a natural biodegradable polysaccharide. In some aspects, one or more bioactive agent(s) can be included in the coating composition. In the coating composition, the bioactive agent can be in mixture with the hydrophobic derivative (but not coupled to the hydrophobic derivative), coupled to the hydrophobic derivative, or both. The bioactive agent can be present in the composition at a concentration that allows formation of a coating or an article with therapeutically useful properties. The amount and type of bioactive agent may be chosen based on the type of hydrophobic derivative present in the composition.

[0150] To illustrate one method of preparing a coating, a composition is prepared by the combining a bioactive agent with a hydrophobic polysaccharide in a suitable solvent. Examples of solvents that can be used include aromatic

compounds such as toluene and xylene, and ethers such as tetrahydrofuran. Other suitable solvents include halogenated alkanes such as methylene chloride and chloroform; and amides such as dimethylformamide (DMF). Combinations of one or more of these or other solvents can also be used. The type of solvent system used can be chosen according to the hydrophobic polysaccharide, the bioactive agent, and any other optional component present in the composition.

[0151] In cases where formation of a coating with a high bioactive agent is desired, the natural biodegradable polysaccharide and the bioactive agent can, in combination, comprise about 90% or greater by weight, 95% or greater by weight, 97.5% or greater by weight, or 99% or greater by weight, of the total solids of the coating composition. In turn, when applied to the surface of an article to be coated, the coating can include these same percentages solids.

[0152] More specifically, in some aspects, bioactive agent is present in an amount in the range of about 10 wt % to about 65 wt % of the solids in the coating or coating composition, and the hydrophobic polysaccharide is present in the range of about 90 wt % to about 35 wt %. In more specific aspects, bioactive agent is present in an amount in the range of about 25 wt % to about 55 wt % of the solids in the coating or coating composition, and the hydrophobic polysaccharide is present in the range of about 75 wt % to about 45 wt %. In even more specific aspects, bioactive agent is present in an amount in the range of about 40 wt % to about 50 wt % of the solids in the coating or coating composition, and the hydrophobic polysaccharide is present in the range of about 60 wt % to about 50 wt %.

[0153] The hydrophobic polysaccharide can optionally be blended with one or more other hydrophobic compounds in a composition for preparation of the coating. The other hydrophobic compounds can be biodegradable polymers. For example, the coating can be prepared using a blend of two or more different hydrophobic polysaccharides. The hydrophobic polysaccharide can differ with regards to one or more of the following aspects: molecular weight, type of pendent group (e.g., type of hydrocarbon segment), and amount of groups pendent from the polysaccharide.

[0154] The hydrophobic polysaccharide can also be blended with different types of biodegradable polymers. Examples include polyesters such as poly(lactic acid) (poly (lactide)), poly(glycolic acid) (poly(glycolide)) poly(lactide-co-glycolide), poly(dioxanone); polylactones such as poly (caprolactone) and poly(valerolactone), copolymers such as poly(glycolide-co-polydioxanone), poly(glycolide-co-trimethylene carbonate), and poly(glycolide-co-caprolactone); poly(3-hydroxybutyrate), poly(3-hydroxyvalerate), poly (tartronic acid), poly(β-malonic acid), poly(propylene fumarate); degradable polyesteramides; degradable polyanhydrides and polyalkeneanhydrides (such as poly(sebacic acid), poly(1,6-bis(carboxyphenoxy)hexane, poly(1,3-bis (carboxyphenoxy)propane); degradable polycarbonates and aliphatic carbonates; degradable polyiminocarbonates; degradable polyarylates; degradable polyorthoesters; degradable polyurethanes; degradable polyphosphazenes; degradable polyhydroxyalkanoates; degradable polyamides; degradable polypeptides; and copolymers thereof.

[0155] Compositions of the invention that include the hydrophobic polysaccharide in an organic solvent can be used to coat the surface of a variety of implantable medical devices. The coating composition (with or without bioactive agent) can be applied to a medical device using standard techniques to cover the entire surface of the device, or a portion of the device surface. If more than one coated layer is applied to a surface, it is typically applied successively. For example, a hydrophobic polysaccharide coated layer can be formed by, for example, dipping, spraying, bushing, or swabbing the coating material on the article 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 the natural biodegradable polysaccharide. The compositions of the present invention are particularly suitable for use in spray coating processes.

[0156] An exemplary spray coating process and apparatus that can be used for coating implantable medical articles using the compositions of the present invention is described in U.S. Patent Publication No. 2004-0062875-A1 (filed Sep. 27, 2002).

[0157] A composition that includes the hydrophobic polysaccharide can be spray coated directly onto the surface of a body member of a medical article, or can be spray coated onto a surface that includes one or more coated layers of material previously formed on the body member. The composition may be spray coated onto a coated layer of material that includes a bioactive agent.

[0158] Other coated layers can include polymers such as methacrylate, acrylate, alkylacrylate, acrylamide, vinylpyrrolidinone, vinylacetamide, or vinyl formamide polymers. These polymers can also include latent reactive groups, such as photoreactive groups.

[0159] In some cases the coated layer that includes the hydrophobic derivative is formed on a base layer. The base layer can serve one or more functions, for example, it can provide an improved surface for the formation of a coated layer that includes the hydrophobic derivative.

[0160] Components of the biodegradable coating can be applied to the medical device using standard techniques to cover the entire surface of the device, or a portion of the device surface. As indicated, the components can be applied to the medical device independently or together, for example, in a composition. The coating formed on the device can be a single layer coating, or a multiple layer coating.

[0161] In some aspects the coating comprises a biocompatible hydrophilic polymer. The biocompatible hydrophilic polymer can increase the rate of release of the bioactive agent from the coating, as compared to an equivalent coating that does not include the biocompatible hydrophilic polymer. The biocompatible hydrophilic polymer can be biodegradable or non-biodegradable. Exemplary biocompatible hydrophilic polymers include poly(ethylene glycol), hydrophilic polysaccharides, polyvinyl pyrrolidones, polyvinyl alcohols, low molecular weight methyl cellulose, hydroxypropyl methyl cellulose (HPMC), and the like.

[0162] The biodegradable hydrophilic polymer is thought to create hydrophilic domains in the coating. These hydrophilic domains are thought to drive fluid into the coating after the coated implantable article has been placed within a subject. In one proposed mechanism, release of the bioactive agent is thought to be promoted by an increase in osmotic pressure with the coating, which forces bioactive agent out of the coating. In another proposed mechanism, release of the bioactive agent is thought to be promoted by the hydrolysis of pendent groups linked via hydrolytically cleavable

ester groups. This decreases the hydrophobicity of the coating, and increases the rate of release of the bioactive agent.

[0163] For example, in some aspects, bioactive agent is present in an amount in the range of about 10 wt % to about 65 wt % of the solids in the coating or coating composition, and the hydrophobic derivative of the natural biodegradable polysaccharide is present in the range of about 70 % to about 35 wt % of the solids in the coating or coating composition, and the biodegradable hydrophilic polymer is present in an amount in the range of about 1 % to about 20 % of the solids in the coating or coating composition In more specific aspects, bioactive agent is present in an amount in the range of about 25 wt % to about 55 wt % of the solids in the coating or coating composition, the hydrophobic derivative is present in the range of about 60 wt % to about 40 wt % of the solids in the coating or coating composition, and the biodegradable hydrophilic polymer is present in an amount in the range of about 5 % to about 15 % of the solids in the coating or coating composition.

[0164] In even more specific aspects, bioactive agent is present in an amount in the range of about 40 wt % to about 50 wt % of the solids in the coating or coating composition, the hydrophobic derivative is present in the range of about 50 wt % to about 40 wt % of the solids in the coating or coating composition, and the biodegradable hydrophilic polymer is present in an amount in the range of about 7.5 % to about 12.5 % of the solids in the coating or coating composition.

[0165] Other optional components can be included in the coating. These components can be included in amounts less than the amounts of hydrophobic polysaccharide or bioactive agent in the coating. These optional components can change or improve the properties of the coating.

[0166] Components that can facilitate the detection of the implanted medical article include colorants, radiopacifying agents, and radioisotopes. The presence of one or more of these components can facilitate detection of the location of article following implantation.

[0167] Another class of optional components is excipients. Excipients can improve the stability of the bioactive agent that is associated with the coating and/or act as a plasticizing agent to change the physical property of the coating. Exemplary excipients include glycerol, diethylene glycol, sorbitol, sorbitol esters, maltitol, sucrose, fructose, invert sugars, corn syrup, and mixtures thereof. The amount and type of excipient(s) can be based on known standards and techniques. Antioxidants can be added to the coating to maintain coating properties, including the stability of the bioactive agent.

[0168] Optional components can also be used to change the elasticity, flexibility, wettability, or adherent properties, (or combinations thereof) of the coating.

[0169] Implantable medical articles that include a biodegradable coating can be treated to sterilize one or more parts of the article, or the entire article. Sterilization can take place prior to using the coated article and/or, in some cases, during implantation of the medical article. For example, a stent with a biodegradable coating can be sterilized before insertion into the body. In some aspects the coated article can be contacted with an aqueous sterilization solution.

[0170] According to some aspects of the invention, bioactive agent is made available to a subject using a method that involves the following steps. One step is implanting at a target site in a subject a medical article having a coating comprising a biodegradable coating comprising a matrix of hydrophobic natural biodegradable polysaccharides and bioactive-agent within the matrix. Another step is allowing the bioactive agent to be released from the coating in the subject following the step of implanting.

[0171] While the step of implanting can be performed to place the coated medical article at a desired location anywhere in the body, an exemplary process involves the placement of a stent having a biodegradable coating in the vasculature.

[0172] Stents with the biodegradable coating as described herein have particular application in the field of coronary angioplasty. As used herein, the terms "stent" and "prosthesis" are used interchangeably to some extent in describing the invention, insofar as the methods, apparatus, and structures of the invention can be utilized not only in connection with an expandable intraluminal vascular graft for expanding partially occluded segments of a vessel, duct, or body passageways, such as within an organ, but can also be utilized for many other purposes as an expandable prosthesis for many other types of body passageways. For example, expandable prostheses can also be used for such purposes as (1) supportive graft placement within blocked arteries opened by transluminal recanalization, but which are likely to collapse in the absence of internal support; (2) similar use following catheter passage through mediastinal and other veins occluded by inoperable cancers; (3) reinforcement of catheter created intrahepatic communications between portal and hepatic veins in patients suffering from portal hypertension; (4) supportive graft placement of narrowing of the esophagus, the intestine, the ureters, the urethra, and the like; (5) intraluminally bypassing a defect such as an aneurysm or blockage within a vessel or organ; and (6) supportive graft reinforcement of reopened and previously obstructed bile ducts. Accordingly, use of the term "prosthesis" encompasses the foregoing usages within various types of body passageways, and the use of the term "intraluminal graft" encompasses use for expanding the lumen of a body passageway. Further, the term "body passageway" encompasses any lumen or duct within the body, such as those previously described, as well as any vein, artery, or blood vessel within the vascular system.

[0173] Coated stents can be adapted for deployment and implantation using conventional methods known in the art and employing percutaneous transluminal catheter devices. Coated stents can be designed for deployment by any of a variety of in situ expansion means, such as an inflatable balloon or a polymeric plug that expands upon application of pressure. For example, the tubular body of the stent can be positioned to surround a portion of an inflatable balloon catheter. The stent, with the balloon catheter inside is configured at a first, collapsed diameter. The stent and the inflatable balloon are percutaneously introduced into a body lumen, following a previously positioned guidewire in an over-the-wire angioplasty catheter system, and tracked by suitable means (such as fluoroscopy) until the balloon portion and associated stent are positioned within the body passageway at the implantation site. Thereafter, the balloon is inflated and the stent is expanded by the balloon portion from the collapsed diameter to a second expanded diameter. After the stent has been expanded to the desired final expanded diameter, the balloon is deflated and the catheter is withdrawn, leaving the stent in place. During placement,

the stent can optionally be covered by a removable sheath or other means to protect both the stent and the vessels.

[0174] For self-expanding stents, the following procedure can be applicable. In order to deliver a stent to the site of a stenotic lesion (implantation site), the external diameter of the stent is reduced so that the stent can easily traverse the blood vessels leading to the implantation site. The stent is disposed within the reduced diameter portion of the vessel. Thus, the stent is reduced by, for example, elongating the stent, allowing for a corresponding reduction in diameter, and maintained in such a reduced diameter or collapsed configuration during the delivery process. Once at the implantation site, the forces tending to reduce the diameter of the stent are released whereby the stent can support and/or dilate the stenotic portion of the vessel.

[0175] In some aspects, the stent can be delivered to an implantation site by placing the reduced diameter stent within a delivery sheath that is in turn fed through a guide catheter through the vasculature to the implantation site. The stent carrying sheath is then advanced from the distal end of the guide catheter over a guide wire into the targeted vessel and to the implantation site (site of a stenotic lesion).

[0176] A second sheath can be provided proximally of the collapsed stent and used to facilitate removal of the stent from the outer sheath. For example, once the sheath has been disposed at the implantation site of a vessel, the inner, proximal sheath is held in place while the outer sheath is retracted or pulled proximally with respect to the stent. Removal of the outer sheath removes the forces that retain the stent in its collapsed configuration and thus allow the stent to self-expand within the stenotic portion of the vessel to support and dilate the vessel walls. The inner sheath prevents the stent from moving proximally with the outer sheath. The inner and outer sheaths as well as the guide wire and guide catheter can then be removed from the vascular system. Alternatively, the inner and outer sheaths can be removed and a balloon catheter fed through the guide catheter over the guide wire and into the expanded stent. The balloon can then be inflated within the stent so as to urge the stent into firm engagement with the walls of the vessel and/or to augment the dilation of the artery effected by the stent alone.

[0177] In some aspects, the stent can be delivered to the implantation site on a balloon catheter. Such balloon catheters are well known and will not be described in more detail here.

[0178] Another exemplary process involves the placement of an ocular article having a biodegradable coating in a portion of the eye.

[0179] An ocular article having a coating formed of hydrophobic derivatives of natural biodegradable polysaccharides can be implanted into a portion of the eye using any suitable method. Typically, the ocular article is delivered using an insertion instrument to provide the coated medical article to the targeted site within the eye. The term "implantation site" refers to the site within a patient's body at which the coated medical article is located during a treatment course according to the invention.

[0180] The ocular article can be placed at an implantation site within the eye tissues. Suitable ocular implants can perform a function and/or provide bioactive agent to any desired area of the eye. For example, an implantation site can be chosen to provide bioactive agent primarily to an anterior segment of the eye (in front of the lens), or to a posterior segment of the eye (behind the lens). Suitable ocular implants can also be utilized to provide bioactive agent to tissues in proximity to the eye, when desired. In some aspects, the ophthalmic article can be configured for placement at an intraocular site, such as the vitreous.

[0181] The vitreous chamber is the largest chamber of the eye and contains the vitreous humor or vitreous. Generally speaking, the vitreous is bound interiorly by the lens, posterior lens zonules and ciliary body, and posteriorly by the retinal cup. The vitreous is a transparent, viscoelastic gel that is 98% water and has a viscosity of about 2-4 times that of water. The main constituents of the vitreous are hyaluronic acid (HA) molecules and type II collagen fibers, which entrap the HA molecules. The viscosity is typically dependent on the concentration of HA within the vitreous. The vitreous is traditionally regarded as consisting of two portions: a cortical zone, characterized by more densely arranged collagen fibrils, and a more liquid central vitreous.

[0182] Therefore, in some aspects, the invention provides methods for placing an ocular article at a site within the body, the site comprising a gel-like material, such as viscoelastic gel.

[0183] In many aspects of the invention, the ocular article is placed in the vitreous. In some aspects, the ocular article can be delivered through the scleral tissue (trans-scleral injection).

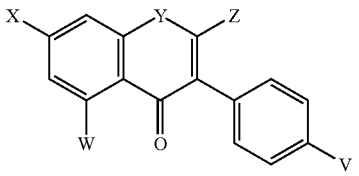
[0184] The ocular article can be used for the treatment of diabetic retinopathy, which is characterized by angiogenesis in the retinal tissue.

[0185] Diabetic retinopathy has four stages. While the ocular article can be delivered to a subject diagnosed with diabetic retinopathy during any of these four stages, it is common to treat the condition at a later stage.

[0186] The first stage is mild nonproliferative retinopathy which is characterized by the appearance of microaneurysms in retinal blood vessels. The second stage is moderate nonproliferative retinopathy which is characterized by blockage of the retinal blood vessels. The third stage is severe nonproliferative retinopathy which is characterized by a more extensive blockage of the retinal blood vessels, which deprive several areas of the retina with their blood supply and results in the formation of new blood vessels in the retina (angiogenesis) in response to this deprivation. The fourth stage is proliferative retinopathy which is characterized by active formation of new blood vessels, which have an abnormal morphology. These abnormally-formed vessels grow along the retinal and vitreal surface and are prone to leak blood, which can result in severe vision loss.

[0187] The treatment of diabetic retinopathy can be accomplished by delivering the ocular article to a target location so that one or more anti-angiogenic factors is released from the ocular article and affects sub-retinal tissue. In some aspects the bioactive agent is an inhibitor of angiogenesis such as anecortave acetate, or a receptor tyrosine kinase antagonist.

[0188] Compounds and methods for treating diabetic retinopathy with a receptor tyrosine kinase antagonist have been described in U.S. Pat. No. 5,919,813. In some aspects, the coated medical article of the present invention comprises a compound of formula I:



wherein V, W and X are selected from the group consisting of hydro, hydroxyl, alkoxy, halo, an ester, an ether, a carboxylic acid group, a pharmaceutically acceptable salt of a carboxylic acid group, and ——SR, in which R is hydrogen or an alkyl group, and Y is selected from the group consisting of oxygen, sulfur, C(OH), and C═O, and Z is selected from the group consisting of hydro and $C(O)OR_1$, wherein R_1 is an alkyl. In some aspects, the alkoxy is a C_1-C_6 alkoxy. In some aspects, the halo is fluorine, chlorine or bromine. In some aspects, the ester is a C_1-C_6 ester. In some aspects, the ether is a C_1-C_6 ether. Pharmaceutically acceptable salts of the carboxylic acid group include sodium and potassium salts. In some aspects, the alkyl groups are C_1-C_6 alkyl groups. In some aspects, the protein tyrosine kinase pathway inhibitor is genistein.

[0189] Exemplary dosage ranges using a compound of formula I are from about 1 mg/kg/day to about 100 mg/kg/day, or more specifically from about 15 mg/kg/day to about 50 mg/kg/day.

[0190] Combination drug delivery strategies can also be carried out for the treatment of diabetic retinopathy. For example, retinal tissue can be treated with one or more neurotrophic factors. Exemplary neurotrophic factors include ciliary neurotrophic factor (CNTF) and glial cell-derived neurotrophic factor (GDNF). In addition neuroprotective agents such as coenzyme Q10, creatine, and minocycline can be delivered from the implant. As an example, minocycline is thought to be a neuroprotective agent (in addition to its role as an antibiotic with anti-inflammatory effects) as it may also prevent the cascade of events leading to programmed cell death (apoptosis).

[0191] The treatment of diabetic retinopathy can be performed by administration of the coated medical article alone, or can be performed with other procedures such as laser surgery and/or vitrectomy.

[0192] The coated medical article can be used for the treatment of uveitis, which is characterized by inflammation of the uvea. The uvea is the layer of the eye between the sclera and the retina and includes the iris, ciliary body, and choroid. The uvea provides most of the blood supply to the retina.

[0193] Forms of uveitis include anterior uveitis, which typically involves inflammation that is limited to the iris (iritis). Another form of uveitis involves inflammation of the pars plana (between the iris and the choroid). Another form of uveitis is posterior uveitis affects primarily the choroid (choroiditis). The ocular article of the present invention can be delivered to a target site in the eye for the treatment of any of these particular conditions.

[0194] The present invention contemplates treating uveitis by delivering one or more anti-inflammatory factors in the sub-retinal space.

[0195] In a more particular aspect of the present invention, steroids, including anti-inflammatory steroids and corticosteroids, are delivered to the sub-retinal space. Exemplary anti-inflammatory steroids and corticosteroids include hydrocortisone, hydrocortisone acetate, dexamethasone 21-phosphate, fluocinolone, medrysone, methylprednisolone, prednisolone 21-phosphate, prednisolone acetate, fluoromethalone, betamethasone, and triamcinolone, or triamcinolone acetonide.

[0196] In an exemplary embodiment, the dosage of the steroid is between about 10 μg and about 500 μg over a period of time in the range of about three to about twelve months. This dosage range is applicable to each of the three following stages of macular degeneration, namely: early onset macular degeneration, atrophic macular degeneration (AMD) and neovascular macular degeneration (NMD).

[0197] The ocular article can also be used for the treatment of retinitis pigmentosa, which is characterized by retinal degeneration. For example, the present invention contemplates treating retinitis pigmentosa by delivering one or more neurotrophic factors in the sub-retinal space.

[0198] The ocular article can also be used for the treatment of age-related macular degeneration (AMD). AMD is characterized by both angiogenesis and retinal degeneration. Specific forms of AMD include, but are not limited to, dry age-related macular degeneration, exudative age-related macular degeneration, and myopic degeneration. The ocular article of the present invention can be delivered to a target site in the eye for the treatment of any of these forms of AMD. As an example, the coated medical article can be used to deliver one or more of the following drugs for the treatment of AMD: anti-VEGF (vascular endothelial growth factor) compounds, neurotrophic factors, and/or anti-angiogenic factors. In some specific aspects, the ocular article is used to release a corticosteriod for the treatment of sub-retinal tissue.

[0199] The ocular article can also be used for the treatment of glaucoma, which is characterized by increased ocular pressure and loss of retinal ganglion cells. The ocular article of the present invention can be delivered to a target site in the eye for the treatment of glaucoma contemplated for the release of one or more neuroprotective agents that protect cells from excitotoxic damage. Such agents include N-methyl-D-aspartate (NMDA) antagonists, cytokines, and neurotrophic factors.

[0200] An ocular article condition can also be treated by delivering the coated medical article to a target location in the eye to release an antiproliferative agent, such as 13-cis retinoic acid, retinoic acid derivatives, 5-fluorouracil, taxol, rapamycin, analogues of rapamycin, tacrolimus, ABT-578, everolimus, paclitaxel, taxane, or vinorelbine.

[0201] An ocular condition can also be treated by delivering the ocular article to a target location in the eye to release a beta adrenergic agent such as isoproterenol, epinephrine, norepinephrine (agonists) and propranolol (antagonist).

[0202] An ocular condition can also be treated by delivering the ocular article to a target location in the eye to release a prostaglandin such as PGE_2 or PGF_2.

[0203] The ocular article of the present invention can also be used for the prophylactic treatment of a subject. In other words, the coated medical article may be provided to a subject even if there has not been a diagnosed existence of a disorder or disease. For example, in more than 50% of cases where AMD occurs in one eye, it will subsequently occur in the unaffected eye within a year. In such cases,

prophylactic administration of a therapeutic medium such as a steroid into the unaffected eye may prove to be useful in minimizing the risk of, or preventing, AMD in the unaffected eye.

[0204] The bioactive agent can be released for a period of time and in an amount sufficient to treat a medical condition in a subject, such as one suffering from a cardiovascular disease or compilation. One distinct advantage of the present invention are that bioactive agents can be released from the coating at a steady rate, meaning that there is not substantial variation in amount of bioactive agent released per day over the bioactive agent release period of the coating. Given this, the coatings of the invention allow for drug delivery that is close to a zero-order release rate. The bioactive agent can also be released in therapeutically effective amounts for treatment of medical conditions.

[0205] In some aspects, the bioactive agent is released at an average rate in the range of 10 ng/day to 10 μg/day. In more specific aspects, the bioactive agent is released at an average rate in the range of 100 ng/day to 7.5 μg/day. In yet more specific aspects, the bioactive agent is released at an average rate in the range of 500 ng/day to 5 μg/day. In yet more specific aspects, the bioactive agent is released at an average rate in the range of 750 ng/day to 2.5 μg/day. In yet more specific aspects, the bioactive agent is released at an average rate of approximately 1 μg/day.

[0206] Another distinct advantage is that the coatings can be prepared having a particularly long bioactive agent release period, in which therapeutically effective amounts of bioactive agent are able to be released at later points during this period. With regard to bioactive agent release, the coating can have a "half-life," which is the period of time at which half of the total amount of bioactive agent that is present in the coating is released during the bioactive agent release period.

[0207] For example, in one aspect, 50% of the amount of bioactive agent present in the coating is released from the coating after a period of 100 days. In this regard, the coating can be used for the treatment of medical conditions wherein bioactive agent is to be released for a period of time of about 3 months or greater, a period of time of about 6 months or greater, a period of time of about 9 months or greater, a period of time of about 12 months or greater, a period of time in the range of about 3 to about 6 months, a period of time in the range of about 3 to about 9 months, a period of time in the range of about 3 to about 12 months, or a period of time in the range of about 3 to about 24 months.

[0208] In some aspects, depending on the properties of the implant, a carbohydrase can promote the degradation of the coating. For example, the groups pendent from the polysaccharide backbone can be released by hydrolytic cleavage, and a portion of the coating can become accessible to a carbohydrase, which can enzymatically digest the polysaccharide and degrade the coating.

[0209] In these aspects, hydrolysis of the ester bond, which can occur non-enzymatically, and enzymatic hydrolysis of the linkages between the monomeric (or dimeric) units of the polysaccharide portion can contribute to degradation of the coating. For example, non-enzymatic hydrolysis can lead to cleavage and loss of the pendent group comprising the hydrocarbon segment from the coating. This loss may lead to a portion of the article becoming more hydrophilic, and subject to attack by a carbohydrase resulting in biodegradation of the polysaccharide, and/or further decomposition of the coating by loss of the polysaccharide from the surface.

[0210] Degradation by a carbohydrase may occur before, during, or/and after the release of the bioactive agent. Examples of carbohydrases that can specifically degrade natural biodegradable polysaccharide coatings include α-amylases, such as salivary and pancreatic α-amylases; disaccharidases, such as maltase, lactase and sucrase; trisaccharidases; and glucoamylase (amyloglucosidase).

[0211] Serum concentrations for amylase are estimated to be in the range of about 50-100 U per liter, and vitreal concentrations also fall within this range (Varela, R. A., and Bossart, G. D. (2005) *J Am Vet Med Assoc* 226:88-92).

[0212] In some aspects, a carbohydrase can be administered to a subject to increase its concentration in the body fluid or tissue surrounding the coated article, so that the carbohydrase may promote the degradation of the implant. Exemplary routes for introducing a carbohydrase include local injection, intravenous (IV) routes, and the like. Alternatively, degradation can be promoted by indirectly increasing the concentration of a carbohydrase in the vicinity of the coated article, for example, by a dietary process, or by ingesting or administering a compound that increases the systemic levels of a carbohydrase.

[0213] In other cases, the carbohydrase can be provided on a portion of the article that is coated. For example the carbohydrase may be released from a portion of the article to promote its own degradation.

[0214] The coating can also be eroded by liberatation of polysaccharides from the surface of the implant. For example, after pendent groups are released from the polysaccharide by hydrolytic cleavage, the polysaccharide can loose its hydrophobic association with the remaining portion of the implant, and be partially or wholly released into fluid or tissue surrounding the implant. Degradation of the liberated polysaccharide by a carbohydrase can take place during or after liberation of the polysaccharide.

[0215] Degradation of the hydrophobic derivatives of the biodegradable polysaccharides of the present invention can result in the release of naturally occurring mono- or disaccharides, such as glucose. These naturally occurring mono- or disaccharides which are common serum components and present little or no immunogenic or toxic risk to the individual.

[0216] Optionally, a lipase can be used in association with the article to accelerate degradation of the bond between the pendent group and the polysaccharide (e.g., ester bond).

[0217] The invention will be further described with reference to the following non-limiting Examples. It will be apparent to those skilled in the art that many changes can be made in the embodiments described without departing from the scope of the present invention. Thus the scope of the present invention should not be limited to the embodiments described in this application, but only by embodiments described by the language of the claims and the equivalents of those embodiments. Unless otherwise indicated, all percentages are by weight.

EXAMPLE 1

[0218] 11 g of dried maltodextrin (GPC, Grain Processing Corporation, Muscatine, Iowa) was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 20 g (0.244 moles, 19.32 mls, Sigma-Aldrich) of 1-methylimidizole followed by 50 g (0.32 moles, 52 mls,

Sigma-Aldrich, Milwaukee, Wis.) of butyric anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then quenched with deionized water. The taffy-like material that precipitated from the quenched reaction mixture was placed in 1,000 MWCO dialysis tubing and dialyzed vs. continuous flow deionized water for three days. After this time the solid product was lyophilized. 23.169 g of a white powdery solid was obtained. The theoretical degree of substitution (DS) was 2.5.

EXAMPLE 2

[0219] 10 g of dried MD was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 23.7 g (0.29 moles, 22.9 mls) of 1-methylimidizole followed by 29.34 g (0.29 moles, 27.16 mls) of acetic anhydride (Sigma-Aldrich, Milwaukee, Wis.) were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid was collected via filtration and dried in vacuo. 15.92 g of a yellow powdery solid was obtained. The theoretical DS was 2.5

EXAMPLE 3

[0220] 10 g of dried MD was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 9.49 g (0.11 moles, 9.17 mls) of 1-methylimidizole followed by 18.19 g (0.11 moles, 18.81 mls) of butyric anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid was collected via filtration and dried in vacuo. 16.11 g of a white powdery solid was obtained. The theoretical DS was 1.

EXAMPLE 4

[0221] 10 g of dried MD was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 14.24 g (0.17 moles, 13.76 mls) of 1-methylimidizole followed by 27.32 g (0.17 moles, 28.25 mls) of butyric anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid was collected via filtration and dried in vacuo. 18.95 g of a white powdery solid was obtained. The theoretical DS was 1.5.

EXAMPLE 5

[0222] 10 g of dried MD was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 18.97 g (0.23 moles, 18.33 mls) of **1**-methylimidizole followed by 36.39 g (0.23 moles, 37.63 mls) of butyric anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid was collected via filtration and dried in vacuo. 19.78 g of a white powdery solid was obtained. The theoretical DS was 2.

EXAMPLE 6

[0223] 10 g of dried polyalditol (GPC, Grain Processing Corporation, Muscatine, Iowa) was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 28.46 g (0.35 moles, 27.5 mls) of 1-methylimidizole followed by 54.58 g (0.35 moles, 56.44 mls) of butyric anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then quenched with deionized water. The reaction mixture was placed in 1,000 MWCO dialysis tubing and dialyzed vs. continuous flow deionized water for three days. After this time the solution was lyophilized. 11.55 g of a white powdery solid was obtained. The theoretical DS was 2.

EXAMPLE 7

[0224] 1 g of dried β-cyclodextrin (Sigma-Aldrich, Milwaukee, Wis.) was dissolved in 10 mls of dimethyl sulfoxide with stirring. When the solution was complete, 5.02 g (0.061 moles, 4.85 mis) of 1-methylimidizole followed by 9.62 g (0.061 moles, 9.95 mls) of butyric anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then quenched with deionized water. The reaction mixture was placed in 1,000 MWCO dialysis tubing and dialyzed vs. continuous flow deionized water for three days. After this time the solution was lyophilized. 234 mg of a white powdery solid was obtained. The theoretical DS was 2.

EXAMPLE 8

[0225] 10 g of dried MD was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 23.7 g (0.29 moles, 22.9 mls) of 1-methylimidizole followed by 37.38 g (0.29 moles, 36.8 mls) of propionoic anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid was collected via filtration and dried in vacuo. 18.49 g of a white powdery solid was obtained. The theoretical DS was 2.5.

EXAMPLE 9

[0226] 10 g of dried MD was dissolved in 100 mls of dimethyl sulfoxide with stirring. When the solution was complete, 9.48 g (0.12 moles, 9.16 mls) of 1-methylimidizole followed by 14.95 g (0.12 moles, 14.73 mls) of propionoic anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one

hour. The solid was collected via filtration and dried in vacuo. 14.32 g of a white powdery solid was obtained. The theoretical DS was 1.

EXAMPLE 10

[0227] 4 g of dried MD was dissolved in 40 mls of dimethyl sulfoxide with stirring. When the solution was complete, 9.48 g (0.12 moles, 9.16 mls) of 1-methylimidizole followed by 24.63 g (0.12 moles, 26.6 mls) of caproic anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid obtained was taffy-like and collected via filtration and dried in vacuo. 7.18 g of a white solid was obtained. The theoretical DS was 2.5.

EXAMPLE 11

[0228] 4 g of dried MD was dissolved in 40 mls of dimethyl sulfoxide with stirring. When the solution was complete, 3.79 g (0.046 moles, 3.7 mls) of 1-methylimidizole followed by 9.85 g (0.046 moles, 10.64 mls) of caproic anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid was collected via filtration and dried in vacuo. 9.02 g of a white powdery solid was obtained. The theoretical DS was 1.

EXAMPLE 12

[0229] 2.0 g of dried MD was dissolved in 10 mls of dimethyl sulfoxide with stirring. 0.751 g (2.3 mmole) decanoic anhydride was dissolved in 3 ml of chloroform. When the solutions were complete 0.188 g (2.3 mmoles, 0.183 mls) of 1-methylimidizole was added to the DMSO/MD solution followed by the addition of the chloroform/anhydride solution and 7.0 ml DMSO. The reaction was stirred for 1 hour at room temperature. The reaction mixture was placed in 1,000 MWCO dialysis tubing and dialyzed vs. continuous flow deionized water for three days. The dialysis tube and contents were placed in 1 liter of acetone/methanol-50/50 (volume) three times for more than 1 hour for each solvent change. The dialysis tube and contents were then placed in 4 liters of acetone/methanol-50/50 (volume) three times for 1 day for each solvent change. The solid from the dialysis tube was dried in vacuo. 1.69 g of a white solid was obtained. The theoretical DS was 0.1.

EXAMPLE 13

[0230] 5.0 g of dried MD was dissolved in 10 mls of dimethyl sulfoxide with stirring. 3.15 g (5.75 mmole) stearic anhydride was dissolved in 3 ml of chloroform. When the solutions were complete 0.472 g (5.75 mmoles, 0.458 mls) of 1-methylimidizole was added to the DMSO/MD solution followed by the addition of the chloroform/anhydride solution and 7.0 ml DMSO. The reaction was stirred for 1 hour at room temperature. The reaction mixture was placed in 1,000 MWCO dialysis tubing and dialyzed vs. continuous flow deionized water for three days. The dialysis tube and contents were placed in 1 liter of acetone/methanol-50/50 (volume) three times for more than 1 hour for each solvent change. The dialysis tube and contents were then placed in 4 liters of acetone/methanol-50/50 (volume) three times for 1 day for each solvent change. The solid from the dialysis tube was dried in vacuo. 6.58 g of a white powdery solid was obtained. The theoretical DS was 0.1.

EXAMPLE 14

[0231] 4 g of dried MD was dissolved in 40 mls of dimethyl sulfoxide with stirring. When the solution was complete, 9.48 g (0.12 moles, 9.16 mls) of 1-methylimidizole followed by 24.63 g (0.12 moles, 26.6 mls) of caproic anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid obtained was taffy-like and collected via filtration and dried in vacuo. 7.18 g of a white solid was obtained. The theoretical DS was 2.5.

EXAMPLE 15

[0232] 4 g of dried MD was dissolved in 40 mls of dimethyl sulfoxide with stirring. When the solution was complete, 9.48 g (0.12 moles, 9.16 mls) of 1-methylimidizole followed by 24.63 g (0.12 moles, 26.6 mls) of heptanoic anhydride were added with stirring at room temperature. The reaction solution was stirred for one hour and was then slowly add to 750 mls of deionized water in a Waring blender. The precipitated solid was collected via filtration, re-suspended in 1 L of deionized water and stirred for one hour. The solid obtained was taffy-like and collected via filtration and dried in vacuo. 7.18 g of a white solid was obtained. The theoretical DS was 2.5.

EXAMPLE 16

[0233] Vacuum oven-dried Polyalditol PD60 (4.10 g), N-hydroxysuccinimide (0.38 g), 4-di(methylamino)pyridine (0.39 g), and 2-propylpentanoic acid (9.01 g; valproic acid) were weighed into a 120 mL amber vial. Anhydrous dimethyl sulfoxide, DMSO, (50 mL) was poured into the vial, purged with nitrogen, and placed on a rotary shaker to dissolve. N,N'-diisopropylcarbodiimide, DIC, (9.47 g) was weighed into a 30 mL amber vial and dissolved with 10 mL of anhydrous DMSO. The DIC solution was poured into the 120 mL amber vial and purged with nitrogen gas. A Teflon stir bar was inserted into the 120 mL vial before being capped and placed on a stir plate to stir overnight at room temperature. After overnight stirring, no visible product was seen and the reaction was placed in a 55° C. oven to stir overnight. The reaction formed two layers after heating overnight and was precipitated into 2 L deionized water while stirring. The yellowish/white solid was vacuum-filtered using a water aspirator and rinsed three times with deionized water (100 mL). The solid precipitate was collected and dried in a vacuum oven at 40° C. overnight. The dried solid was organic soluble (tetrahydrofuran, methylene

chloride). A 50 mg/mL solution in THF was prepared and tested by dip coating onto a clean Pebax rod giving a uniform, off-white coating.

EXAMPLE 17

[0234] Vacuum oven-dried Polyalditol PD60 (4.10 g), N-hydroxysuccinimide (0.38 g), 4-di(methylamino)pyridine (0.39 g), and o-acetylsalicylic acid, ASA, (11.26 g) were weighed into a 120 mL amber vial. Anhydrous dimethyl sulfoxide (50 mL) was poured into the vial, purged with nitrogen, and placed on a rotary shaker to dissolve. N,N'-diisopropylcarbodiimide, DIC, (9.47 g) was weighed into a 30 mL amber vial and dissolved with 10 mL of anhydrous DMSO. The DIC solution was poured into the 120 mL amber vial and purged with nitrogen gas. A Teflon stir bar was inserted into the 120 mL vial before being capped and placed on a stir plate to stir overnight at room temperature. After overnight stirring, no visible product was seen and the reaction was placed in a 55° C. oven to stir overnight. The reaction formed a viscous, orange material after heating overnight and was precipitated into 2 L deionized water while stirring. The orange solid was vacuum-filtered using a water aspirator and rinsed once with acetone (25 mL) followed by three times with deionized water (100 mL). The solid precipitate was collected and dried in a vacuum oven at 40° C. overnight. The dried solid was organic soluble (tetrahydrofuran, methylene chloride).

[0235] Stainless steel stents were coated with the polyalditol-ASA polymer. Half of the coated stents were balloon expanded. Expanded and unexpanded coated stents were evaluated by SEM. No evidence of cracking or delamination was observed.

EXAMPLE 18

Release of Lidocaine from Stainless Steel Stents

[0236] A solution was prepared in 15 mls of THF containing 200 mgs of poly(butylmethacrylate) (PBMA) with an approximate weight average molecular weight of 337 kD, 200 mgs poly (ethylene-co-vinyl acetate) (PEVA) with a vinyl acetate content of 33% (w/w), and 200 mgs lidocaine.

[0237] Stainless steel stents were prepared for coating as follows. The stents were cleaned by soaking in a 6% (by volume) solution of ENPREP-160SE (Cat. #2108-100, Enthone-OMI, Inc., West Haven, Conn.) in deionized water for 1 hour. After soaking, the parts were then rinsed several times with deionized water. After rinsing, the stents were soaked for 1 hour at room temperature in 0.5% (by volume) methacryloxypropyltrimethoxy silane (Cat.# M6514, Sigma Aldrich, St. Louis, Mo.) made in a 50% (by volume) solution of deionized water and isopropyl alcohol. The stainless steel wires were allowed to drain and air dry. The dried stents were then placed in a 100° C. oven for 1 hour.

[0238] After oven-drying, the stents were placed in a parylene coating reactor (PDS 2010 LABCOTER™ 2, Specialty Coating Systems, Indianapolis, Ind.) and coated with 2 g of Parylene C (Specialty Coating Systems, Indianapolis, Ind.) by following the operating instructions for the LABCOTER™ system. The resulting Parylene C coating was approximately 1-2 μm thickness.

[0239] Solutions for coatings were sprayed onto the Parylene C treated stents using an IVEK sprayer (IVEK Dispenser 2000, IVEK Corp., North Springfield, Vt.) mounting a nozzle with a 1.0 mm (0.04 inch) diameter orifice and pressurized at 421.84 g/cm.sup.2 (6 psi). The distance from the nozzle to the stent surface during coating application was 5 to 5.5 cm. A coating application consisted of spraying 40 μL of the coating solution back and forth on the stent for 7 seconds. The spraying process of the coating was repeated until the amount of lidocaine on the stent was estimated to be around 200 micrograms. The coating compositions on the stents were dried by evaporation of solvent, approximately 8-10 hours, at room temperature (approximately 20° C. to 22° C.). After drying, the coated stents were re-weighed. From this weight, the mass of the coating was calculated, which in turn permitted the mass of the coated polymer(s) and lidocaine to be determined.

[0240] Three solutions were prepared in THF; each solution was prepared at 50 mg/mL. The three solutions were comprised of maltodextrin-propionate (MD-Prop) (from Example 8), maltodextrin-acetate (MD-Ace) (from Example 2), and maltodextrin-caproate (MD-Cap) (from Example 10). Each of these solutions was coated onto PBMA/PEVA/lidocaine coated stents as described above. The spraying process was repeated until the amount of MD polymer was estimated to be around 500 micrograms.

[0241] The Elution Assay utilized herein was as follows. Phosphate buffered saline (PBS, 10 mM phosphate, 150 mM NaCl, pH 7.4, aqueous solution) was pipetted in an amount of 3 mL to 10 mL into an amber vial with a Teflon™ lined cap. A wire or coil treated with the coating composition was immersed into the PBS. A stir bar was placed into the vial and the cap was screwed tightly onto the vial. The PBS was stirred with the use of a stir plate, and the temperature of the PBS was maintained at 37° C. with the use of a water bath. The sampling times were chosen based upon the expected or desired elution rate. At the sampling time point, the stent was removed from the vial and placed into a new vial containing fresh PBS. A UV/VIS spectrophotometer was used to determine the concentration of the drug in the PBS solution that previously contained the stent treated with the coating composition. The cumulative amount of drug eluted versus time was plotted to obtain an elution profile. The elution profiles are illustrated graphically in FIG. **1**.

EXAMPLE 19

Barrier Coating on Degradable Magnesium Alloy Coupon

[0242] 1 cm×0.75 cm strips were cut from a sheet of magnesium alloy (96% magnesium, 3% aluminum, 1% zinc; Goodfellow Cambridge Lmtd., Huntington, England). 1000 mg of MD-Cap DS 2.5 (from Example 10) was dissolved in THF at **5** room temperature. Half of the magnesium alloy strips were coated with MD-Cap DS 2.5 by dipping the bottom half of each strip into the polymer solution, removing the strip, allowing the strip to dry, dipping the top half of the strip into the polymer solution, removing the strip and allowing the strip to dry. This procedure was repeated **4** times. Both the coated and uncoated strips were subsequently weighed. Coated and uncoated 10 strips are placed individually into vials and 2 mls of phosphate buffered saline (PBS) pH 7.4 is added to each vial. The vials were sealed and placed in a 37° C. environmental chamber. At various time points the vials were removed from the chamber and the strips visually observed; approximate estimates of the amount of each strip remaining were made and are shown in Table 1.

TABLE 1

Time	Strip	Observations
0	uncoated	100% remaining
0	coated	100% remaining
8 hrs	uncoated	Slight pitting of surface
8 hrs	coated	Nothing discernable
24 hrs	uncoated	Clear pitting of surface
24 hrs	coated	Nothing discernable
48 Hrs	uncoated	Heavy pitting, edges dissolving
48 hrs	coated	Slight pitting of surface
5 days	uncoated	Approx. 30% dissolved
5 days	coated	Clear pitting of surface
6 days	uncoated	Approx. 40% dissolved
6 days	coated	Edges dissolving
7 days	uncoated	Approx. 80% dissolved
7 days	coated	Approx 5% dissolved
8 days	uncoated	Approx. 90% dissolved
8 days	coated	Approx 10% dissolved
9 days	uncoated	100% dissolved
9 days	coated	Approx 35% dissolved

On day 9 the coated strips were removed from their vials and weighed; they had retained an average of 63.0% of their original mass.

EXAMPLE 20

Rapamycin Eluting Stents in a Pig Model

Stent Preparation

[0243] Stainless steel stents were prepared for coating as follows. The stents were cleaned by soaking in a 6% (by volume) solution of ENPREP-160SE (Cat. #2108-100, Enthone-OMI, Inc., West Haven, Conn.) in deionized water for 1 hour. After soaking, the parts were then rinsed several times with deionized water. Stents were coated with MD-caproate from Example 10 (Hex 2.5 MD lot 2795-159) with and without rapamycin. The polymer was stored room temperature before use.

[0244] Coating solutions were prepared in THF by mixing freshly-prepared stock solutions of polymer and rapamycin. Polymer-only coating solutions contained 50 mg/mL of the polymer. Polymer/drug coating solutions contained a total solid load of 50 mg/mL, of which 50 wt % was rapamycin (i.e., 25 mg/mL polymer+25 mg/mL rapamycin). All coating solutions were passed through a 10 μm filter before being used for coating.

[0245] Coating was performed with an ultrasonic spray system (Gen III) in a Class 10,000 clean room. Coated parts were dried under a flow of N2 at room temperature overnight. Each of the solutions atomized well and produced acceptable coatings on the stents.

[0246] Coated stents (50% rapamycin) were crimped onto balloon catheters. Stents were crimped at ambient temperature and humidity. No sleeve was present during crimping; the stent coatings were in direct contact with the Delrin crimping head. An effort was made to prevent strut-to-strut contact during the crimping process. After crimping, the stent/catheter assemblies were packaged, labeled, sterilized via EtO. Following sterilization, the assemblies were placed under vacuum overnight at room temperature to remove residual EtO.

[0247] The crimped stents were immersed in PBS at 37° C. for 5 minutes. The balloon was then inflated to a pressure of 9 atm, held for 5 s, and the pressure was released. The catheter and expanded stent were removed from the PBS and rinsed with DI water. Stents that did not easily fall off the balloons were removed with a tweezers. Stents were dried under a flow of nitrogen at room temperature. Dried stents were examined with optical microscopy and imaged with SEM to assess the mechanical properties of the coatings. Balloons were examined with optical microscopy to determine whether any coating material remained on the balloon. In general, coatings with and without rapamycin exhibited good mechanical properties

In vitro Drug Release and Coating Studies

[0248] Elution measurements were conducted in 2 different solutions: PBS and PBS supplemented with a physiologic concentration of amylase at 37° C. Each stent was placed in a conical glass vial to which 4 mL of the appropriate solution was added. The vials were placed in a shaking incubator during elution. At determined intervals, the eluent was completely removed from the vial and sampled for rapamycin content. 4 mL of fresh solution was then placed in the vial. A robotic system assisted in the collection of samples and replacement of solution. Samples for drug content were placed into a 96-well UV plate and rapamycin was detected by UV absorbance at 279 nm. Each polymer coating was run in triplicate. Stent weights were taken concurrently to determine the rate of coating degradation.

[0249] Rapamycin eluted from the stents with a first order release rate over 40 days. Approximately 50% of the coating remained on the stents after 40 days. Stent coatings containing drug and coated stents placed in enzyme solution lost coating weight at a faster rate than those without drug and those placed in buffer only.

Porcine System

[0250] The purpose of this study was to use the porcine coronary and peripheral artery model to assess the biological affects of the MD-caproate degradable polymer, with and without rapamycin. Angiographic, histomorphometric and histopathologic variables were evaluated at predetermined time intervals.

[0251] Excessive neointimal growth has been identified as a major cause of late failure of the percutaneous transluminal coronary angioplasty (PTCA) procedure. Rapamycin, a potent anti-neoplastic, promotes the assembly of microtubules and inhibits the tubulin disassembly process to prevent cell proliferation. Rapamycin delivered from coronary stents (drug eluting stent) has been shown to inhibit neointimal growth in studies conducted in both animal models and in humans. Concern has been expressed about the long-term effects of durable drug eluting polymers that have been coated on stents.

[0252] Both male and female domestic Yorkshire cross-bred swine were used in this study. All animals were acclimated, fasted, underwent a physical examination and received pre-procedure medications prior to stent implantation.

Experimental Design

[0253] Animals underwent the swine stent injury model described by Schwartz, et al. (2002) Circulation 218:669-696. Following a preliminary angiogram, stents were implanted in each of the 3 main coronary arteries (right coronary artery (RCA), left anterior descending (LAD), or

left circumflex (LCX), based on angiographic assessment of the artery diameter and length (one stent per vessel). Vessel section were limited to reference size of 2.6 mm to 3.4 mm based on visual estimation and online QCA at the time of implant.

[0254] The artery segment was selected based on the ability of the vessel to accommodate the diameter and length of the stent. The implantation pressure was varied according to the balloon compliance curve, included in the packaging, to achieve a target stent/vessel ratio of 1.10:1 with a range of 1.05-1.20:1

[0255] Prior to implantation, the animal was designated for a specific cohort (1 month or 3 months). At the predetermined time point, stents were harvested.

[0256] After animal preparation was completed, the femoral artery was accessed using a percutaneous approach. A 7F introducer arterial sheath was placed and advanced into the artery. After a baseline ACT was recorded, an initial bolus of heparin (100 IU/kg IV) was given. Additional doses of heparin were administered to maintain an ACT of ≧250 seconds. Doses given were based on the ACT levels. ACT was tested approximately every 15-30 minutes.

Implant Procedures

[0257] Under fluoroscopic guidance, a 6F or appropriate guide catheter was inserted through the sheath and advanced to the appropriate location. After placement of the guide catheter, angiographic images of vessels were obtained with contrast media to identify the proper location for the deployment site. Quantitative angiography was performed to determine the appropriate vessel size for implantation.

[0258] The stents were implanted in each of the three major branches of the coronary arteries (RCA, LAD, and LCX). An effort was made to evenly distribute the experimental group and controls to the different vessels.

[0259] After visualization of the arterial anatomy, a target segment ranging from 2.6 mm to 3.4 mm mid-segment diameter was chosen, and a 0.014" guidewire was inserted into the chosen artery. QCA was then performed to accurately document the reference diameter for stent placement.

[0260] Each stent delivery system was prepared by applying vacuum to the balloon port; contrast/flush solution (50:50) was introduced by releasing the vacuum. The stent was introduced into the appropriate artery by advancing the stented balloon catheter through the guide catheter and over the guidewire to the deployment site. The balloon was inflated at a steady rate to a pressure sufficient to target a balloon:artery ratio of 1.10:1 with a range of 1.05-1.20:1 and held for approximately 20 seconds. A contrast injection was performed during full inflation to demonstrate occlusion with the balloon. After the target balloon:artery ratio had been achieved for approximately 20 seconds, vacuum was applied to the inflation device in order to deflate the balloon. Complete balloon deflation was verified with fluoroscopy. The delivery system was then slowly removed.

Explant Procedures

[0261] At the designated endpoint, the animals were weighed, sedated, and anesthetized. An arterial sheath was introduced in the femoral vessels and heparin was administered as previously described. A guiding catheter was placed and advanced under fluoroscopic guidance into the coronary arteries. After placement of the guide catheter into the appropriate coronary ostium, angiographic images of the vessel were taken to evaluate the stented sites. At the end of the terminal angiography procedure, the animals were euthanized.

[0262] Following gross assessment, a trained technician performed excision of the whole heart. Dissection of the implanted coronary arterial bed with subsequent removal of the stent and neointima was performed prior to perfusion fixation when stents were explanted for surface characterization. The neointima was weighed then frozen and held at −70 C. Hearts were perfused with saline or Lactated Ringers solution until the fluid ran clear and pressure perfusion-fixed with 10% buffered formalin until there was a color change in the tissue. Whole hearts and any additional tissues were shipped to the study pathologist for complete histopathological analysis. A group of stents was retrieved for surface analysis.

Histopathological Analyses of 28-Day Explants

Coated Stents without Drug

[0263] The stents are well expanded against the arterial wall and lumens are patent with no evidence of thrombus formation, aneurysms, or malapposition. The neointima growth consists primarily of smooth muscle cells and proteoglycan/collagen matrix with organized layers near the lumen. In the majority of stents, injury to the arterial wall is minimal, except for the mid section from CV17805 (896, LCx), which shows 5 struts penetrating into the medial wall with extensive macrophage infiltration and the LCx stent from CV17802 (animal No. 887), which shows extensive granulomas. Organized layers of smooth muscle cells are found more towards the lumen while more disorganized clusters of smooth muscle cells are found near struts. Fibrin accumulation around stent struts is generally absent. Giant cells around stent struts are minimal. Re-endothelialization of luminal surfaces is near complete with very rare adherent inflammatory cells. Inflammation around stent struts was absent or minimal except for stents with granulomas to include all sections from CV17802 (887, LCx), which showed severe granulomatous reactions in all sections consisting of eosinophils, macrophages and giant cells. Hemorrhage around stent stuts is generally mild. The non-stented proximal and distal segments generally showed balloon overstretch injury evidenced by accumulated proteoglycan matrix (bluish-green staining on Movat) in the medial wall and mild neointimal growth.

Coated Stents with Drug

[0264] The stents are well expanded against the arterial wall and lumens are patent with no evidence of thrombus formation, aneurysms, or malapposition. The neointimal growth is mild consisting primarily of smooth muscle cells and proteoglycan/collagen matrix with organized layers near the lumen. Injury to the arterial wall is minimal. Organized layers of smooth muscle cells are found more towards the lumen while more disorganized clusters of smooth muscle cells are found near struts. Fibrin accumulation around stent struts is generally mild to moderate, which in a few struts was extensive. There are occasional giant cells near stent struts. Re-endothelialization of luminal surfaces is near complete with very rare adherent inflammatory cells. Inflammation around stent struts was generally minimal. Hemorrhage around stent stuts is present and generally mild.

The non-stented proximal and distal segments generally showed balloon overstretch injury evidenced by accumulated proteoglycan matrix (bluish-green staining on Movat) in the medial wall and mild neointimal growth.

Uncoated Stents

[0265] The stents are well expanded against the arterial wall and lumens are patent with no evidence of thrombus formation, aneurysms or malapposition. The struts are generally covered by mild to moderate neointimal growth consisting of organized layers of smooth muscle cells towards the lumen while more disorganized clusters of smooth muscle cells are found near struts together with proteoglycan matrix. There is little fibrin accumulation around stent struts with minimal giant cell infiltration and overall inflammation is minimal. Re-endothelialization of luminal surfaces is near complete with rare adherent inflammatory cells. The non-stented proximal and distal segments generally showed balloon overstretch injury evidenced by accumulated proteoglycan matrix (bluish-green staining) in the medial wall and mild neointimal growth.

Surface Analysis of Explanted Stents

[0266] Explanted stents were examined using SEM. The coated explanted stents showed an adherent polymer covering approximately 30-50% of the stent surface. Coated stents with rapamycin generally showed more polymer degradation than coated stents without rapamycin.

What is claimed is:

1. An implantable medical article comprising a biodegradable bioactive-agent releasing coating, the coating comprising a matrix of hydrophobic derivatives of natural biodegradable polysaccharides and bioactive-agent within the matrix, wherein the coating is capable of releasing bioactive agent following placement of the medical article in a subject.

2. The implantable medical article of claim **1** wherein the matrix comprises hydrophobic derivatives having an average molecular weight of 100,000 Da or less.

3. The implantable medical article of claim **2** wherein the matrix comprises hydrophobic derivatives having an average molecular weight of 50,000 Da or less.

4. The implantable medical article of claim **3** wherein the matrix comprises hydrophobic derivatives having an average molecular weight of 25,000 Da or less.

5. The implantable medical article of claim **4** wherein the matrix comprises hydrophobic derivatives having an average molecular weight in the range of 2000 Da to 20,000 Da.

6. The implantable medical article of claim **5** wherein the matrix comprises hydrophobic derivatives having an average molecular weight in the range of 4000 Da to 10,000 Da.

7. The implantable medical article of claim **1** wherein the hydrophobic derivatives comprise a poly-α(1→4)glucopyranose backbone.

8. The implantable medical article of claim **1** wherein the hydrophobic derivatives comprise a plurality of groups pendent from a polysaccharide backbone, the groups comprising a hydrocarbon segment selected from the group consisting of linear, branched, and cyclic C_2-C_{18} groups.

9. The implantable medical article of claim **8** wherein the hydrocarbon segment is selected from the group consisting of linear, branched, and cyclic C_4-C_{10} groups.

10. The implantable medical article of claim **9** wherein the hydrocarbon segment is selected from the group consisting of linear, branched, or cyclic C_5-C_7 groups.

11. The implantable medical article of claim 10 wherein the plurality of groups pendent from the polysaccharide backbone provide a degree of substitution in the range of 2-3.

12. The implantable medical article of claim **11** wherein the hydrocarbon segment is a C_6 aromatic group.

13. The implantable medical article of claim **9** wherein the hydrocarbon segment is selected from the group consisting of branched C_4-C_{10} alkyl groups.

14. The implantable medical article of claim **13** wherein the plurality of groups pendent from the polysaccharide backbone provide a degree of substitution in the range of 0.5-1.5.

15. The implantable medical article of claim **1** wherein the hydrophobic derivatives have a Tg of 35° C. or greater.

16. The implantable medical article of claim **15** wherein the hydrophobic derivatives have a Tg in the range of 40° C. to 90° C.

17. The implantable medical article of claim **1** wherein the hydrophobic derivatives are present in the coating in an amount in the range of 35 wt % to 90 wt %.

18. The implantable medical article of claim **17** wherein the hydrophobic derivatives are present in the coating in an amount in the range of 35 wt % to 60 wt %.

19. The implantable medical article of claim **1** wherein the bioactive agent is present in the coating in an amount in the range of 10 wt % to 65 wt %.

20. The implantable medical article of claim **1** wherein the coating is formed on the surface of an implantable ocular device.

21. The implantable medical article of claim **1** wherein the coating is formed on the surface of an implantable intravascular device.

22. The implantable medical article of claim **1** wherein the bioactive agent is coupled to a polysaccharide backbone of the hydrophobic derivatives via a hydrolyzable ester bond.

23. The implantable medical article of claim **1** wherein the coating further comprises a biocompatible hydrophilic polymer.

24. The implantable medical article of claim **23** wherein the biocompatible hydrophilic polymer is selected from the group consisting of group consisting of poly(ethylene glycol), hydrophilic polysaccharides, polyvinyl pyrrolidones, polyvinyl alcohols, low molecular weight methyl cellulose, hydroxypropyl methyl cellulose (HPMC).

25. A method for delivering a bioactive agent to a subject comprising steps of:

implanting at a target site in a subject an implantable medical article comprising a biodegradable bioactive-agent releasing coating, the coating comprising a matrix of hydrophobic derivatives of natural biodegradable polysaccharides and bioactive agent within the matrix, and

allowing the bioactive agent to be released from the coating in the subject following the step of implanting.

26. The method of claim **25** wherein the step of implanting comprises delivering the article to a portion of the eye.

27. The method of claim **25** wherein the step of allowing, the bioactive agent released comprises a carboxylate group.

28. The method of claim **25** wherein the bioactive agent is coupled to a polysaccharide backbone of the hydrophobic derivatives via a hydrolyzable ester bond.

29. A method for preparing a biodegradable bioactive-agent releasing coating on a medical article comprising steps of:

preparing a coating composition comprising hydrophobic derivatives of natural biodegradable polysaccharides and bioactive-agent; and

applying the coating composition on a surface of a medical article to form a coating, wherein the bioactive-agent is capable of being released from the coating following implantation of the medical article in a subject.

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