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(54) **PDLLA STENT COATING**

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(57) **ABSTRACT**

An amorphous PDLLA stent coating for drug delivery is disclosed.

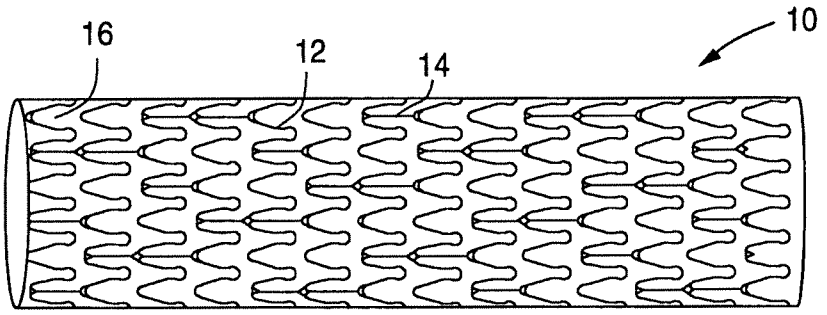

FIGURE 1
(PRIOR ART)

PDLLA STENT COATING

CROSS-REFERENCE

[0001] This application is a continuation of application Ser. No. 11/022,228, filed on Dec. 23, 2004, which in turn is a continuation-in-part of application Ser. No. 09/894,293, filed on Jun. 27, 2001. The entire disclosures of both applications are incorporated into this document by reference.

BACKGROUND

[0002] Blood vessel occlusions are commonly treated by mechanically en-hancing blood flow in the affected vessels, such as by employing a stent. Stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically stents are capable of being compressed, so that they can be inserted through small lumens via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in the patent literature disclosing stents include U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, and U.S. Pat. No. 4,886,062 issued to Wiktor.

[0003] FIG. **1** illustrates a conventional stent **10** formed from a plurality of struts **12**. The plurality of struts **12** are radially expandable and interconnected by connecting elements **14** that are disposed between adjacent struts **12**, leaving lateral openings or gaps **16** between adjacent struts **12**. Struts **12** and connecting elements **14** define a tubular stent body having an outer, tissue-contacting surface and an inner surface.

[0004] Stents are used not only for mechanical intervention but also as vehi-cles for providing biological therapy. Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. Local delivery of a therapeutic substance is a preferred method of treatment because the substance is concentrated at a specific site and thus smaller total levels of medication can be administered in comparison to systemic dos-ages that often produce adverse or even toxic side effects for the patient.

[0005] One method of medicating a stent involves the use of a polymeric car-rier coated onto the surface of the stent. A composition including a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent by immersing the stent in the composition or by spraying the composition onto the stent. The solvent is allowed to evaporate, leaving on the stent strut surfaces a coating of the polymer and the therapeutic substance impregnated in the polymer.

[0006] A shortcoming of the above-described method of medicating a stent is the potential for coating defects due to the large amount of liquid composition applied to the relatively small surface area of the stent. The liquid composition can flow, wick, and collect as the amount of composition on the stent increases during the coating process. As the solvent evaporates, the excess composition hardens, leaving the excess coating as clumps or pools on the struts or webbing between the struts.

[0007] Another shortcoming of the above-described method of medicating a stent is the potential for loss of the therapeutic substance from the coating or produc-tion of a coating that does not provide for a suitable residence time of the substance at the implanted region. Initial portions of a liquid composition containing a therapeutic substance sprayed onto a stent adhere to the stent surface. However, as the liquid composition continues to be applied to the stent, layers of the composition are formed on top of one another. When exposed to the solvent in the upper layers, the therapeutic substance in the lower layers can be re-dissolved into the upper layers of the composition or extracted out from the coating. Having the therapeutic substance maintained in merely the upper regions of the coating provides for a short residence time of the substance at the implanted region, as the therapeutic substance will be quickly released. Prolonged residence times in situ may be desirable for a more effective treatment of a patient.

[0008] The present invention addresses such problems by providing methods of coating implantable devices.

SUMMARY

[0009] A stent is disclosed comprising a coating, the coating consisting of a poly(D,L-lactic acid) (PDLLA) and a macrocyclic drug, wherein the PDLLA has a degree of crystallinity of less than 20 percent, the measurement being by weight of the amount of polymer that is in the form of crystallites as measured by differential scanning calorimetry, wherein the coating has a thickness of 0.05 microns to 10 microns, and wherein the stent on which the coating is disposed is made from a bioabsorbably polymer.

BRIEF DESCRIPTION OF THE FIGURES

[0010] FIG. **1** illustrates a conventional stent.

DETAILED DESCRIPTION

[0011] This document incorporates by this reference the entire disclosure of U.S. patent application Ser. No. 09/894,293, which was filed on Jun. 27, 2001.

[0012] For ease of discussion, the methods detailed herein will be described with reference to coating a stent. However, the device or prosthesis coated in accordance with embodiments of the present invention may be any suitable medical substrate that can be implanted in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any de-sign. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), high nitrogen stainless steel, e.g., BIODUR 108, cobalt chrome alloy L-605, "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. In some embodiments, the implantable device is chosen to specifically exclude any one or any combination of self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and

endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). In some embodiments, the implantable device is not a catheter. In some embodiments in which the implantable device can be chosen to be a catheter, the implantable device is chosen not to be a catheter liner.

[0013] The methods of some embodiments of the current invention comprise adjusting the temperature of an implantable portion of a medical device to a target temperature, which is always non-ambient, and then coating the implantable portion of the medical device with a coating substance. In some embodiments, adjusting occurs such that the increase or decrease in temperature only occurs before applying the coating substance begins. In other embodiments, adjusting occurs such that heating or cooling starts before and continues during the applying step or the adjusting and applying steps occur substantially together.

[0014] Different invention embodiments employ different "adjusting" profiles. For instance, in some profiles, the implantable device is adjusted to the target temperature before applying a coating substance and then applying occurs (with or without some amount of temperature decrease before crimping); alternatively, the implantable device is adjusted to the target temperature before applying a coating substance and maintained at or near the target temperature during applying; alternatively, applying is started, the implantable medical device is adjusted to the target temperature, and applying is completed. In some embodiments, applying begins before the implantable device has reached the target temperature and continues until or after the target temperature has been reached.

[0015] For purposes of this disclosure, ambient temperature is the temperature of the implantable device when it has not been purposely heated or cooled. In al-ternative embodiments, ambient temperature is room temperature, 25-30° C., 20-30° C., 20-25° C., 23-27° C. or 10-30° C. Similarly, for purposes of this disclosure, a target temperature is a temperature numerically different from ambient temperature. In some embodiments, the difference between the target temperature and ambient is brought about by purposely heating or cooling the implantable device.

[0016] A target temperature is chosen based on the characteristics of the components of the coating substance. For instance, if the solvent of the coating substance is non-volatile or has a low volatility, the target temperature can be chosen to be above ambient temperature to improve the evaporation rate. Conversely, if the coating substance solvent is volatile, the target temperature can be chosen to be below ambient temperature to lower the evaporation rate. The identity of the solvent is not the only characteristic upon which a target temperature can be based. For instance, if the coating substance comprises a therapeutic substance, the target temperature can be chosen to minimize thermal degradation of the therapeutic substance. Alternatively, if a polymer is used in the coating substance, the target temperature can be chosen above Tg of the polymer to improve its flow characteristics during deposition. In other embodiments, if the solvent of the coating substance has a high boiling point, the target temperature can be chosen to be above ambient temperature to improve the evaporation rate. Conversely, if the coating substance solvent has a low boiling point, the target temperature can be chosen to be below ambient temperature to lower the evaporation rate. Similarly, if the solvent is likely to freeze at ambient temperature during the applying step, the target temperature can be chosen to maintain it in a molten state to facilitate its removal. Those of ordinary skill in the art will be able to identify other characteristics of components of the coating substance that can be improved by applying the substances to an implantable device that is at a non-ambient target temperature.

[0017] In some embodiments, the target temperature is chosen to be above ambient temperature if the solvent is non-volatile or has low volatility. In some embodiments, non-volatile and having low volatility take their standard meanings as rec-ognized by those of ordinary skill in the art. In these or other embodiments, non-volatile and having low volatility means that the solvent has a volatility such that it does not substantially evaporate in a scientifically or commercially reasonable time as that time would be understood by one of ordinary skill in the art.

[0018] In some embodiments, non-volatile or having a low volatility means that when a solution composed of at least the solvent is applied to an implantable device the solvent does not substantially evaporate within 30 sec, 60 sec, 2 min, 5 min, 10 min, 15 min, 30 min, or 60 min at ambient temperature and pressure. In some embodiments, the target temperature is chosen to be below ambient temperature if the solvent is volatile. In some embodiments, volatile takes its standard meanings as rec-ognized by those of ordinary skill in the art. In these or other embodiments, volatile means the solvent substantially evaporates fast enough to compromise the coating in a scientifically or commercially unreasonable manner as that would be understood by one of ordinary skill in the art. In some embodiments, volatile means that when a solution composed of at least the solvent is applied to an implantable device the solvent substantially evaporates within <30 sec, <20 sec, <15 sec, <10 sec, <8 sec, <5 sec, <4 sec, <3 sec, <2 sec, or <1 sec at ambient temperature and pressure. In some embodiments, the target temperature is chosen to be below the decomposition region for a therapeutic substance.

[0019] In some embodiments that use coating substances to form primer layers, the target temperature can be chosen higher than ambient. In some embodiments that use coating substances to form topcoat layers, the target temperature can be chosen close to ambient or lower than ambient temperature.

[0020] In some embodiments, adjusting the temperature of the implantable device comprises adjusting the temperature to a target temperature and then letting the temperature fluctuate thereafter.

[0021] In some embodiments, adjusting the temperature of the implantable medical device to a target temperature means adjusting the temperature to within ±1° C., ±2° C., ±3° C., ±4° C., ±5° C., ±6° C., ±7° C., ±8° C., ±9° C., ±10° C., ±12° C., ±15° C., or ±20° C. of the target temperature before, during, or after the applying step begins.

[0022] "Adjusting" the temperature of the medical device comprises placing the object that is to have its temperature adjusted into thermal contact with a heat source. For purposes of this disclosure, thermal contact with a heat source means heat source arrangement vis-à-vis the object so that energy would flow or be carried from the heat source to the object. Thermal contact is a generic term at least encompassing an arrangement of the object such that radiation, conduction, or convection from the heat source would transfer energy. In some embodiments, thermal contact is defined to exclude any of radiation, conduction, convection, or any combination of these. Furthermore no invention embodiments use a convection oven or an ultrasound energy source.

[0023] In some embodiments, "maintained near the target temperature" means that the temperature of the implantable device, when it contacts the coating substance, is the same as the target temperature or within ±1° C., ±2° C., ±3° C., ±4° C., ±5° C., ±6° C., ±7° C., ±8° C., ±9° C., ±10° C., ±12° C., ±15° C., or ±20° C. of the target temperature.

[0024] In some embodiments, "maintained at the target temperature during the applying step" means keeping the temperature of the implantable device the same as the target temperature or within ±1° C., ±2° C., ±3° C., ±4° C., ±5° C., ±6° C., ±7° C., ±8° C., ±9° C., ±10° C., ±12° C., ±15° C., or ±20° C. of the target temperature.

[0025] The applying step forms a coating on an implantable medical device such as a stent; it is accomplished in some embodiments by spraying a composition onto the stent. A spray apparatus, such as EFD 780S spray device with VALVEMATE 7040 control system (manufactured by EFD Inc., East Providence, R.I.), can be used to apply the composition to the stent. EFD 780S spray device is an air-assisted external mixing atomizer. The composition is atomized into small droplets by air and uniformly applied to the stent surfaces. The atomization pressure can be maintained at a range of about 5 psi to about 20 psi. The droplet size depends on factors such as vis-cosity of the solution, surface tension of the solvent, and atomization pressure. Other types of spray applicators, including air-assisted internal mixing atomizers and ultrasonic applicators, can also be used for the application of the composition.

[0026] During the application of the composition, the stent can be rotated about the stent's central longitudinal axis. Rotation of the stent can be from about 0.1 rpm to about 300 rpm, more narrowly from about 1 rpm to about 10 rpm. By way of example, the stent can rotate at about 3 rpm. The stent can also be moved in a linear direction along the same axis. The stent can be moved at about 1 mm/second to about 12 mm/second, for example about 6 mm/second, or for a minimum of at least two passes (i.e., back and forth past the spray nozzle).

[0027] The flow rate of the composition from the spray nozzle can be from about 0.01 mg/second to about 1.0 mg/second, more narrowly about 0.1 mg/second. Only a small percentage of the composition that is delivered from the spray nozzle is ultimately deposited on the stent. By way of example, when a composition is sprayed to deliver about 1 mg of solids, only about 100 micrograms or about 10% of the solids sprayed will likely be deposited on the stent. Multiple repetitions for applying the composition can be performed, wherein each repetition can be, for example, about 0.5 second to about 5 seconds in duration. In these or other embodiments, the steps can be repeated 2-100, 2-50, 30-100, 20-50, 50-100, or greater than 100 times. The amount of coating applied by each repetition can be about 1 microgram/cm^2 (of stent surface) to about 50 micrograms/cm^2, for example less than about 20 micrograms/cm^2 per 1-second spray.

[0028] Each repetition can be followed by removal of a significant amount of the solvent(s). The removal of the solvent(s) can be performed following a waiting period of about 0.1 second to about 5 seconds after the application of the coating composition so as to allow the liquid sufficient time to flow and spread over the stent surface before the solvent(s) is removed to form a coating. The waiting period is particularly suitable if the coating composition contains a volatile solvent, such as solvents having boiling points >130° C. at ambient pressure, since such solvents are typically removed quickly.

[0029] The applying step excludes immersing the temperature-adjusted implantable device into the coating substance.

[0030] Removal of the solvent(s) can be induced by the application of a warm gas. The application of a warm gas between each repetition prevents coating defects and minimizes interaction between the active agent and the solvent. Any suitable gas can be employed, examples of which include air or nitrogen. The temperature of the warm gas can be from about 25° C. to about 200° C., more narrowly from about 40° C. to about 90° C. The flow speed of the gas can be from about 0.5 $feet^3$/second (0.01 $meters^3$/second) to about 50 $feet^3$/second (1.42 $meters^3$/second), more narrowly about 2.5 $feet^3$/second (0.07 $meters^3$/second) to about 15 $feet^3$/second (0.43 $meters^3$/second). The gas can be applied for about 1 second to about 100 seconds, more narrowly for about 2 seconds to about 20 seconds. By way of example, warm gas applications can be performed at a temperature of about 60° C., at a flow speed of about 10 $feet^3$/second, and for about 10 seconds.

[0031] In one embodiment, the stent can be warmed to a temperature of from about 35° C. to about 80° C. prior to the application of the coating composition so as to facilitate faster removal of the solvent(s). The particular temperature selected depends, at least in part, on the particular active agent employed in the coating composition. By way of example, pre-heating of the stent prior to applying a composition containing actinomycin D should be performed at a temperature not greater than about 55° C. Pre-heating is particularly suitable for embodiments in which the solvent(s) employed in the coating composition has a high boiling point, i.e., volatile solvents having boiling points of, for example, >130° C. at ambient pressure (e.g., dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMAC)).

[0032] Any suitable number of repetitions of applying the composition followed by removing the solvent(s) can be performed to form a coating of a desired thickness or weight. Excessive application of the polymer can, however, cause coating defects. In embodiments in which the coating composition contains a volatile solvent, a waiting period of from about 0.1 second to about 20 seconds can be employed between solvent removal of one repetition and composition application of the subsequent repetition so as to ensure that the wetting rate of the coating composition is slower than the evaporation rate of the solvent within the composition, thereby pro-moting coating uniformity.

[0033] Operations such as wiping, centrifugation, or other web clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to the physical removal of excess coating from the surface of the stent; and centrifugation refers to rapid rotation of the stent about an axis of rotation. The excess coating can also be vacuumed off of the surface of the stent.

[0034] In accordance with one embodiment, the stent can be at least partially pre-expanded prior to the application of the composition. For example, the stent can be radially expanded about 20% to about 60%, more narrowly about 27% to about 55%—the measurement being taken from the stent's inner diameter at an expanded position as compared to the inner diameter at the unexpanded position. The expansion of the stent, for increasing the interspace between the stent struts during the application of the composition, can further prevent "cob web" formation between the stent struts.

[0035] A final heat treatment can be conducted to remove essentially all of the solvent(s) from the composition on the stent. The heat treatment can be conducted at about 30° C. to

about 200° C. for about 15 minutes to about 16 hours, more narrowly at about 50° C. to about 100° C. for about 1 hour to about 4 hours. By way of example, the heat treatment can be conducted at about 75° C. for 1 hour. The temperature of ex-posure should not adversely affect the characteristics of the active agent or of the coating. The heating can be conducted in an anhydrous atmosphere and at ambient pressure. The heating can, alternatively, be conducted under a vacuum condition. It is understood that essentially all of the solvent(s) will be removed from the composition but traces or residues can remain blended in the coating.

[0036] By way of example, and not limitation, the coating, referred to herein as the primary or reservoir coating, can have a thickness of about 0.05 microns to about 10 microns. The particular thickness of the coating is based on the type of procedure for which the stent is employed and the amount, if any, of active agent that is desired to be delivered. Applying a plurality of reservoir coating layers, containing the same or different active agents, onto the stent can further increase the amount of the active ingredient to be carried by the stent, without causing coating defects.

[0037] In accordance with one embodiment, the coating substance can include a solvent and a polymer dissolved in the solvent. The coating substance can also include active agents, radiopaque elements, or radioactive isotopes. Representative examples of polymers that can be used to coat a stent include ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL), poly(hydroxyvalerate); poly(L-lactic acid); polycaprolactone; poly(lactide-co-glycolide); poly(hydroxybutyrate); poly(hydroxybutyrate-co-valerate); polydioxanone; polyorthoester; polyanhydride; poly(glycolic acid); poly(D,L-lactic acid); poly(glycolic acid-co-trimethylene carbonate); polyphosphoester; polyphosphoester urethane; poly(amino acids); cyanoacrylates; poly(trimethylene carbonate); poly (iminocarbonate); copoly(ether-esters) (e.g. PEO/PLA); polyalkylene oxalates; polyphosphazenes; biomolecules, such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid; polyurethanes; silicones; polyesters; polyolefins; polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as poly-vinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl mono-mers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; polyurethanes; rayon; ray-on-triacetate; cellulose; cellulose acetate; cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

[0038] In some embodiments, the polymer or the processing conditions of the method are selected such that the polymer is non-crystalline. A crystalline polymer is one in which upon analysis a detectable pattern may be observed when using conventional x-ray scattering techniques. Such conventional techniques are disclosed, for example, in "The Structure of Crystalline Polymers", Tadokoro, H. (Wiley Interscience, 1979). The degree of crystallinity of a polymer is the measurement by weight of the amount of polymer that is in the form of crystallites, as measured by differential scanning calorimetry. For purposes of this disclosure, a polymer that is non-crystalline has a degree of crystallinity of less than about 20 percent.

[0039] "Solvent" is defined as a liquid substance or composition that is compatible with the polymer and is capable of dissolving the polymer at the concentration desired in the composition. Examples of solvents include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, acetone, water (buffered saline), xylene, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, isopropanol admixed with water, N-methylpyrroli-dinone, toluene, and combinations thereof.

[0040] The therapeutic agent can inhibit vascular, smooth muscle cell activi-ty. More specifically, the therapeutic agent can aim at inhibiting abnormal or inappro-priate migration or proliferation of smooth muscle cells to prevent, inhibit, reduce, or treat restenosis. The therapeutic agent can also include any substance capable of ex-erting a therapeutic or prophylactic effect in the practice of the present invention. Useful therapeutic agents can include therapeutic agents selected form antibiotics; anticoagulants; antifibrins; antiinflammatories; antimitotics; antineoplastics; antioxi-dants; antiplatelets; antiproliferatives; antithrombins; and their combinations. Other useful therapeutic agents include actinomycin D or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, Wis. 53233; or COSMEGEN available from Merck); dactinomycin; actinomycin IV; actinomycin I_1; actinomycin X_1; actinomycin C_1; paclitaxel; docetaxel; aspirin; sodium heparin; low molecular weight heparin; hirudin; argatroban; forskolin; vapiprost; prostacyclin; prostacyclin analogs; dextran; D-phe-pro-arg-chloromethylketone (synthetic antithrombin); dipyridamole; glycoprotein IIb/IIIa platelet membrane receptor antagonist; recombinant hirudin; thrombin inhibitor (available from Biogen); 7E-3B® (an antiplatelet drug from Centocor); methotrexate; azathioprine; vincristine; vinblastine; fluorouracil; adriamycin; mutamycin; angiopeptin (a somatostatin analog from Ibsen); angiotensin converting enzyme inhibitors; CAPTOPRIL (available from Squibb); CI-LAZAPRIL (available from Hoffman-LaRoche); LISINOPRIL (available from Merck & Co., Whitehouse Station, N.J.); calcium channel blockers; Nifedipine; colchicinefib-roblast growth factor (FGF) antagonists; histamine antagonist; LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck & Co.); mon-oclonal antibodies (such as PDGF receptors); nitroprusside; phosphodiesterase inhibitors; prostaglandin inhibitor (available from Glazo); Seramin (a PDGF antagonist); serotonin blockers; thioprotease inhibitors; triazolopyrimidine (a PDGF antagonist); nitric oxide; alpha-interferon; genetically engineered epithelial cells; dexamethasone; estradiol; clobetasol propionate; cisplatin; insulin sensitizers; receptor tyrosine kinase inhibitors; carboplatin; Rapamycin; 40-O-(2-hydroxy)ethyl-rapamycin, or a functional analog or structural derivative thereof; 40-O-(3-hydroxy)propyl-rapamycin; 40-O-2-(2-hydroxy)ethoxyethyl-rapamycin and their combinations.

[0041] Individual embodiments exist in which the therapeutic agent is selected to specifically exclude any one of or

any combination of the therapeutic agents or therapeutic agent families described above.

[0042] Some invention embodiments comprise a therapeutic agent or therapeutic agent combination, and some require a therapeutic agent or combination of therapeutic agents. Of the therapeutic agents specifically listed above, some invention embodiments exclude a single or any combination of these therapeutic agents.

[0043] Examples of radiopaque elements include, but are not limited to, gold, tantalum, and platinum. An example of a radioactive isotope is P^{32}. Sufficient amounts of such substances may be dispersed in the composition such that the substances are not present in the composition as agglomerates or flocs.

[0044] The methods for coating an implantable device, such as a stent, according to embodiments of the present invention, can be used to create a multi-layer structure that can include any one or any combination of the following four layers:

[0045] (a) a primer layer;

[0046] (b) a drug-polymer layer (also referred to as "reservoir" or "reservoir layer") or a polymer-free drug layer; and

[0047] (c) a topcoat layer, which is likewise drug containing or drug free.

[0048] (d) a finishing layer, for biocompatibility possessing biobeneficial properties.

[0049] In some embodiment, an optional primer layer can be formed prior to the primary or reservoir coating to increase the retention of the primary or reservoir coating on the surface of the stent, particularly metallic surfaces such as stainless steel. The primer layer can act as an intermediary adhesive tie layer between the surface of the device and a reservoir coating carrying an active agent, allowing for the quantity of the active agent to be increased in the reservoir coating.

[0050] To form an optional primer layer on the surface of the stent, an embodiment of the above-described composition that is free from active agents is applied to the surface of the stent. Ethylene vinyl alcohol copolymer, for example, adheres very well to metallic surfaces, particularly stainless steel. Accordingly, the copolymer provides for a strong adhesive tie between the reservoir coating and the surface of the stent. With the use of thermoplastic polymers such as, but not limited to, ethylene vinyl alcohol copolymer, polycaprolactone, poly(lactide-co-glycolide), and poly(hydroxybutyrate), the deposited primer composition should be exposed to a heat treatment at a temperature range greater than about the glass transition temperature (T_g) and less than about the melting temperature (T_m) of the selected polymer. Unex-pected results have been discovered with treatment of the composition under this temperature range, specifically strong adhesion or bonding of the coating to the metallic surface of the stent. The prosthesis should be exposed to the heat treatment for any suitable duration of time that will allow for the formation of the primer layer on the surface of the stent and for the evaporation of the solvent employed. By way of example and not limitation, the optional primer layer can have a thickness of about 0.01 microns to about 2 microns. The application of the primary or reservoir coating should be performed subsequent to the drying of the optional primer layer.

[0051] In another embodiment, an optional diffusion barrier can be formed over a reservoir coating containing an active agent to help control the rate at which the active agent is released from the coated stent. An embodiment of the composition, free from any active agents, can be applied to a selected portion of the primary or reservoir coating subsequent to the drying of the reservoir coating. Application of the composition and evaporation of the solvent to form the diffusion barrier can be accomplished via embodiments of the above-described method of the present invention. The diffusion barrier can have a thickness of about 0.2 microns to about 10 microns. It is understood by one of ordinary skill in the art that the thickness of the diffusion barrier is based on factors such as the type of stent, the type of procedure for which the stent is employed, and the rate of release that is desired. As described above with reference to the primary or reservoir coating, a final heat treatment can be conducted to remove essentially all of the solvent(s) from the optional diffusion barrier.

[0052] Either of the four layers or any combination of them can be formed using invention methods.

EXAMPLES

[0053] The embodiments of the present invention will be illustrated by the following set forth examples, which are being given by way of illustration only and not by way of limitation. All parameters and data are not to be construed to unduly limit the scope of the embodiments of the invention.

Example 1

[0054] Four 8 mm Multi-Link TETRA stents (available from Guidant Corporation) were coated using embodiments of the method of the present invention. The stents were cleaned by sonication in water, followed by sonication in isopropanol. The stents were dried at 70° C. and plasma cleaned in an argon plasma chamber.

[0055] Each unexpanded stent was positioned on a mandrel such that the mandrel contacted the stent at its opposing ends. An EFD 780S spray device with VALVEMATE 7040 control system (manufactured by EFD Inc., East Providence, R.I.) was used to apply the coating compositions to the stents. The spray nozzle was adjusted to provide a distance from the nozzle tip to the outer surface of the stent of approximately 4.5 cm and a spray angle of approximately 90° relative to the horizontal stents. The atomization pressure was set to be maintained throughout the coating process at 20 psi.

[0056] Each stent was passed under the spray nozzle for about 2 seconds. A composition containing 2% (w/w) poly-n-butyl methacrylate (PBMA) 337K in cyclo-hexanone:ethyl acetate (1:1) was sprayed onto one stent. A composition containing 2% (w/w) PBMA 649K in cyclohexanone:ethyl acetate (1:1) was sprayed onto two stents. A composition containing 2% (w/w) PBMA 857K in cyclohexanone:ethyl acetate (1:1) was sprayed onto one stent. Each stent was rotated about the stent's central longitudinal axis at a speed of 3 rpm during coating. After a waiting period of 1 second following the application of the respective compositions, warm air of approximately 80° C. was directed from an air gun onto each stent for 15 seconds to remove most of the solvents. The spraying-blowing cycle was repeated to deposit thirty-four layers on each stent, with a wait time of 5 seconds between each cycle. The coated stent was allowed to dry for about 60 minutes under vacuum conditions in an oven at a temperature of about 70° C. Each of the four coated stents had a uniform, smooth coating. In addition, the stent sprayed with 2% (w/w) PBMA 857K in cyclohexa-none:ethyl acetate (1:1)

was submitted for a simulated use test and was found to have good mechanical properties, no cracking, and good coating adhesion.

Example 2

[0057] An 8 mm Multi-Link TETRA stent was coated using embodiments of the method of the present invention. The stent was cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 15 minutes. The stent was dried and plasma cleaned in a plasma chamber.

[0058] A composition containing 2% (w/w) poly-n-butyl methacrylate (PBMA) and 2% (w/w) quinoline yellow dye in chloroform:cyclohexanone (9:1) was prepared.

[0059] The unexpanded stent was positioned on a mandrel such that the mandrel contacted the stent at its opposing ends. An EFD 780S spray device with VALVEMATE 7040 control system was used to apply the coating composition to the stent. The spray nozzle was adjusted to provide a distance from the nozzle tip to the outer surface of the stent of 1.25 inches (3.18 cm) and a spray angle of approximately 90° relative to the horizontal stent. The atomization pressure was set to be maintained throughout the coating process at 15 psi.

[0060] The stent was passed under the spray nozzle for about 1 second. The stent was rotated about the stent's central longitudinal axis at a speed of 3 rpm during coating. Warm air of approximately 100° C. was directed from an air gun onto the stent for 4 seconds to remove most of the solvents. The spraying-heating cycle was repeated to deposit forty layers on the stent, depositing about 300 micrograms of coating. The coated stent was allowed to dry for about 3 hours under vacuum conditions at a temperature of about 75° C. The coated stent had a uniform, smooth coating with an estimated dye content of about 130 micrograms or 43% of the total amount of coating deposited.

Example 3

[0061] An 8 mm Multi-Link TETRA stent was coated using embodiments of the method of the present invention. The stent was cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 15 minutes. The stent was dried and plasma cleaned in a plasma chamber.

[0062] A primer composition containing 2% (w/w) poly-n-butyl methacrylate (PBMA) was prepared. A reservoir composition containing 2% (w/w) PBMA and 2.7% (w/w) ethyl eosin dye in methanol:cyclohexanone (1:1) was also prepared. In addition, a diffusion barrier composition containing 2% (w/w) PBMA was prepared.

[0063] The unexpanded stent was positioned on a mandrel such that the mandrel contacted the stent at its opposing ends. An EFD 780S spray device with VALVEMATE 7040 control system was used to apply the various compositions to the stent. The spray nozzle was adjusted to provide a distance from the nozzle tip to the outer surface of the stent of 1.25 inches (3.18 cm) and a spray angle of approximately 90° relative to the horizontal stent. The atomization pressure was set to be maintained throughout the coating process at 15 psi. The stent was rotated about the stent's central longitudinal axis at a speed of 3 rpm during coating.

[0064] The primer composition was applied to the stent by passing the stent under the spray nozzle for about 0.75 second. Warm air of approximately 100° C. was directed from an air gun onto the stent for 8 seconds to remove most of the solvents and form a primer layer on the stent. The reservoir composition was then applied to the primered stent by passing the stent under the spray nozzle for about 0.75 second. Warm air of approximately 100° C. was directed from an air gun onto the stent for 4 seconds to remove most of the solvents. The spraying-heating cycle was repeated to deposit forty layers on the stent, depositing about 419 micrograms of the reservoir coating. The coated stent was allowed to dry for about 3 hours under vacuum conditions at a temperature of about 75° C. The barrier layer composition was then applied to the reservoir-coated stent by passing the stent under the spray nozzle for about 0.75 second. Warm air of approximately 100° C. was directed from an air gun onto the stent for 4 seconds to remove most of the solvents. The spraying-heating cycle was repeated to deposit about 70 micrograms of the diffusion barrier. The coated stent was allowed to dry overnight under vacuum conditions at a temperature of about 75° C. The coated stent had a uniform, smooth coating with an estimated dye content of about 224 micrograms or 53% of the total amount of coating deposited.

Example 4

[0065] An 8 mm Multi-Link TETRA stent was coated using embodiments of the method of the present invention. The stent was cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 15 minutes. The stent was dried and plasma cleaned in a plasma chamber.

[0066] A composition containing 2% (w/w) poly-n-butyl methacrylate (PBMA) and 2% (w/w) quinoline yellow dye in chloroform:cyclohexanone (9:1) was prepared.

[0067] The unexpanded stent was positioned on a mandrel such that the mandrel contacted the stent at its opposing ends. An EFD 780S spray device with VALVEMATE 7040 control system was used to apply the composition to the stent. The spray nozzle was adjusted to provide a distance from the nozzle tip to the outer surface of the stent of 1.25 inches (3.18 cm) and a spray angle of approximately 90° relative to the horizontal stent. The atomization pressure was set to be maintained throughout the coating process at 15 psi.

[0068] The stent was passed under the spray nozzle for about 1.5 second. The stent was rotated about the stent's central longitudinal axis at a speed of 3 rpm during coating. Warm air of approximately 100° C. was directed from an air gun onto the stent for 4 seconds to remove most of the solvents. The spraying-heating cycle was repeated to deposit 3 layers on the stent, depositing about 115 micrograms of coating. The coated stent was allowed to dry for about 3 hours under vacuum conditions at a temperature of about 75° C. The coated stent had a uniform, smooth coating with an estimated dye content of about 38 micrograms or 33% of the total amount of coating deposited.

Example 5

[0069] To determine the maximum amount of coating that could be deposited on an 8 mm stent without visible webbing, a Multi-Link TETRA stent was coated using the same coating composition and parameters as described in Example 4. The spraying-heating cycle was repeated until 790 micrograms of coating had been deposited on the stent, at which time no webbing was observed.

Example 6

[0070] An 8 mm Multi-Link TETRA stent was coated using embodiments of the method of the present invention. The

stent was cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 15 minutes. The stent was dried and plasma cleaned in a plasma chamber.

[0071] A composition containing 2% (w/w) poly-n-butyl methacrylate (PBMA) and 2% (w/w) solvent blue dye in chloroform:cyclohexanone (9:1) was prepared.

[0072] The unexpanded stent was positioned on a mandrel such that the mandrel contacted the stent at its opposing ends. An EFD 780S spray device with VALVEMATE 7040 control system was used to apply the composition to the stent. The spray nozzle was adjusted to provide a distance from the nozzle tip to the outer surface of the stent of 1.25 inches (3.18 cm) and a spray angle of approximately 90° relative to the horizontal stent. The atomization pressure was set to be maintained throughout the coating process at 15 psi.

[0073] The stent was passed under the spray nozzle for about 1.5 seconds. The stent was rotated about the stent's central longitudinal axis at a speed of 3 rpm during coating. Warm air of approximately 100° C. was directed from an air gun onto the stent for 4 seconds to remove most of the solvents. The spraying-heating cycle was repeated to deposit about 130 micrograms of coating. The coated stent was allowed to dry for about 3 hours under vacuum conditions at a temperature of about 75° C. The coated stent had a uniform, smooth coating with a estimated dye content of about 85 micrograms or 66% of the total amount of coating deposited.

[0074] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from the embodiments of this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of the embodiments of this invention. Additionally, various embodiments have been described above. For convenience's sake, combinations of aspects (such as monomer type or gas flow rate) composing invention embodiments have been listed in such a way that one of ordinary skill in the art may read them exclusive of each other when they are not necessarily intended to be exclusive. But a recitation of an aspect for one embodiment is meant to disclose its use in all embodiments in which that aspect can be incorporated without undue experimentation. In like manner, a recitation of an aspect as composing part of an embodiment is a tacit recognition that a supplementary embodiment exists that specifically excludes that aspect.

[0075] Moreover, some embodiments recite ranges. When this is done, it is meant to disclose the ranges as a range, and to disclose each and every point within the range, including end points. For those embodiments that disclose a specific value or condition for an aspect, supplementary embodiments exist that are otherwise identical, but that specifically exclude the value or the conditions for the aspect.

What is claimed is:

1. A stent comprising a coating, the coating consisting of a poly(D,L-lactic acid) (PDLLA) and a macrocyclic drug, wherein the PDLLA has a degree of crystallinity of less than 20 percent, the measurement being by weight of the amount of polymer that is in the form of crystallites as measured by differential scanning calorimetry, wherein the coating has a thickness of 0.05 microns to 10 microns, and wherein the stent on which the coating is disposed is made from a bioabsorbable polymer.

2. The stent of claim **1**, wherein the drug is rapamycin.

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